Guide to the quality and safety of ORGANS FOR TRANSPLANTATION

European Committee (Partial Agreement) on Organ Transplantation (CD-P-TO)

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Guide to the quality and safety of organs for transplantation

8th Edition

European Directorate for the Quality of Medicines & HealthCare

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Foreword

Founded in 1949, the Council of Europe is the eldest and largest of all European institutions and now numbers 46 member states.[1] One of its founding principles is that of increasing co-operation between member states to improve the quality of life of European citizens. In this context of intergovernmental co-operation, the Council of Europe has consistently addressed ethical problems in the field of health. One of the most important ethical principles enshrined by the Council of Europe is the non-commercialisation of substances of human origin: blood, organs, tissues and cells.

Work on transplantation at the Council of Europe is co-ordinated by the European Directorate for the Quality of Medicines & HealthCare (EDQM). This directorate is the key European organisation involved in the harmonisation, co-ordination, standardisation, regulation and quality control of medicines, blood transfusion, transplantation, pharmaceuticals, pharmaceutical care and consumer health, as well as cosmetics and food packaging.

Organ transplantation has progressed during recent decades in a way that nobody would have imagined in earlier years. Still the demand for transplantable organs far outweighs the available supply. This has important consequences for health, because organ transplantation is the best, and frequently the only available treatment for end-stage organ failure. Kidney transplantation is also more cost-effective compared with renal replacement therapies with dialysis, even in low-resource environments. Transplantation of human organs also entails the transfer of biological material between individuals and hence the risk of disease transmission from donor to recipient, which must be controlled by the application of appropriate donor screening and selection criteria. Comprehensive quality systems in the transplantation setting must also be in place to guarantee the best possible outcomes.

Guidance and standards

Since 2002, the European Committee (Partial Agreement) on Organ Transplantation of the Council of Europe (CD-P-TO) has been publishing guidance dealing with quality and safety aspects of the donation and transplantation of organs, tissues and cells. This is the 8th edition of the *Guide to the quality and safety of organs for transplantation*. The Guide collates updated information to provide professionals with the most recent advances in the field, as well as technical guidance to ensure the safety and quality of human organs intended for transplantation. It is essential that all stakeholders concerned – professionals involved in identifying possible organ donors, co-ordinators managing the process of donation after death and that of living donation, professionals responsible for the allocation and clinical use of human organs, quality managers of the donation and transplantation process and Health Authorities responsible for the oversight of donation and

1 The Russian Federation ceased to be a member of the Council of Europe as of 16 March 2022, following a decision of the Committee of Ministers to exclude the Russian Federation from the Council of Europe. Rights of representation of Belarus to participate as observer or in any other capacity in meetings and activities of the Committee of Ministers of the Council of Europe or in any of its subsidiary organs were suspended on 17 March 2022.

transplantation programmes – have easy access to this information. This Guide addresses that need by supporting them on a practical level to improve the rate of successful and safe organ transplantation.

Technical guidance on the donation and human application of tissues and cells of human origin has now been moved to a dedicated *Guide to the quality and safety of tissues and cells for human application*, currently in its 5th edition. For blood and blood products, the readers can refer to the Council of Europe *Guide to the preparation, use and quality assurance of blood components*, currently in its 20th edition.

This Guide contains instructions considered to be minimum standards because they align with the Council of Europe's fundamental principles and the relevant European Union (EU) Directives in the field. It provides assistance for those states outside the EU that consider adopting the EU requirements into their regulations. These minimum standards state 'what must be done'. However, this Guide goes beyond these standards by providing additional advice, based on best practice consistent with current scientific knowledge and expert opinion. It describes background information that should be considered in policy decisions, as well as in educational initiatives, by explaining the 'why and how'. It also refers to developments that have yet to be incorporated into EU directives, thereby providing advance information and recommendations regarding developments in the field. Throughout this Guide, the use of the word 'must' indicates mandatory compliance, in alignment with Council of Europe treaties and EU directives, whereas the use of the word 'should' indicates recommended compliance in accordance with good practice.

Terminology

When addressing organ donation after death, this guide uses the terms donation after brain death (DBD) and donation after the circulatory determination of death (DCD). This distinction must not be interpreted as a deviation from the unified concept of death. The fundamental criterion of life and death is a dependence on the functionality of the brain. The ultimate determinant of death is the irreversible cessation of brain functions, which may result from a devastating brain injury or from the cessation of circulation to the brain. Death can be determined based on the irreversible cessation of brain functions (i.e., brain death) or the permanent cessation of circulation – to the brain.

The authors of the Guide acknowledge the limitations of the terminology used, but have kept these two terms and their abbreviations because of their widespread use and for the sake of simplicity. Therefore, the term DBD is used to describe the donation process after death has been determined based on the irreversible cessation of brain functions. The term DCD is used to refer to the donation process after death has been determined based on the permanent cessation of circulation to the brain. The Guide intentionally avoids terms that have become obsolete, such as "donation after cardiac death", "donation after circulatory death" or "non heart beating donation". The Guide also uses the terms *in situ* and *ex situ* for preservation strategies and avoids the terms *in vivo* and *ex vivo*, to clarify that preservation strategies are performed before (*in situ*) or after (*ex situ*) the recovery of organs from a person who has been declared dead.

Changes in the 8th edition

In this 8th edition, all chapters have been thoroughly revised according to the state of the art, new and important chapters have been added, and some innovations have been introduced in the preparation of the chapters.

In order to be able to produce evidence-based recommendations where appropriate, a set of clinical questions was formulated for Chapter 5, Management of the potential donor, and Chapter 11, Organ procurement, preservation and transport. The PICOS approach (population; intervention; comparator; outcomes; study design) was used to formulate these clinical questions. The questions, as identified by the working group, were sent to the Center for Evidence in Transplantation (CET) that undertook a systematic review of the literature and provided a summary of findings. This exercise has allowed to provide more robust recommendations on selected aspects from these two chapters of the Guide. The work undertaken by the CET is presented as Appendices, where the clinical question, the PICOS formulation, the search strategy, the summary of findings and the conclusions are detailed.

In addition, a new section has been included at the end of most chapters: a research agenda. This agenda identifies those fundamental topics for which evidence is insufficient or non-existent and that should be given priority in research initiatives. Chapter 2, Identification and referral of possible deceased organ donors, on this fundamental phase of the deceased donation pathway, addresses challenging practices such as elective non-therapeutic ventilation and admission to the intensive care unit (ICU) to incorporate donation into end-of-life care,

describing best practice in this field. Chapter 3, Determination of death by neurologic criteria, has been thoroughly revised and updated and is considered, like Chapter 4, Family approach and consent/authorisation for *post mortem* organ donation, as being of great value. Chapter 3, Determination of death by neurologic criteria provides a detailed description of the physical examinations and ancillary tests necessary for the diagnosis of death by neurological criteria, including situations such as anoxia, where the usual ancillary tests may pose challenges. Chapter 4 describes the current European legal frameworks for consent and authorisation of organ donation, and best practice in supporting relatives of deceased organ donors and communicating bad news, including the timing of communication.

Chapter 5, Management of the potential donor, has been updated, based on current knowledge in the field. An algorithm has been included, covering the whole process from identification of the potential donor until they become a donor, and the section on nutritional support has been expanded.

Chapter 6, General donor characterisation, assessment and selection criteria, has been revised; it includes a flowchart of the donation process and indicates what chapter of the guide is useful for each step. It also includes a detailed description of imaging techniques. Chapter 7, Specific organ characterisation, assessment and selection criteria, provides the information required for the evaluation of each organ individually considered.

Chapter 8, Risk of transmission of infectious diseases, has been fully revised to include up-to-date developments in the field of emerging pathogens, including Covid-19. The screening algorithms for an extensive list of pathogens have been updated. The chapter also takes into account the impact of new direct-acting antiviral agents in the treatment of hepatitis C virus infection and has updated recommendations on the use of organs from donors infected by this virus. It also addresses the use of organs from HIV-positive donors. Chapter 9, Risk of transmission of cancer, has been entirely reviewed to provide current evidence for assessment of the risk of transplanting organs from donors with a past or present history of malignancies. Among others, two new valuable additions to this chapter are a review of malignancies in the recipient caused by donor oncogenic viruses and a review of donors with a genetic predisposition to cancer. Chapter 10, Risks related to the use of organs from donors with other conditions and diseases, has also been revised, providing recommendations about the use of organs from donors with conditions such as inherited diseases or autoimmune diseases and from donors who have previously received an organ transplant.

Chapter 11, Organ procurement, preservation and transport, has been thoroughly reviewed, providing up-to-date information on organ procurement and *in situ* and *ex situ* preservation techniques, including those that should apply to DCD.

Chapter 12, Donation after the circulatory determination of death (DCD), and Chapter 13, Living donation, deal with topics that require special consideration of procedures, which differ greatly from those applied to the process of DBD. As living donation and DCD are expanding in the European landscape, these two chapters are expected to be of great added value and have been revised extensively. Chapter 12 includes a detailed description of best practice in the realisation of the DCD pathway, both uncontrolled DCD (donation from persons who die following an unsuccessfully resuscitated cardiac arrest) and controlled DCD (donation from persons who die following the decision to withdraw life-sustaining therapies that are no longer deemed beneficial to the patient). It also includes, for the very first time, a reference to DCD in the context of medically-assisted death or euthanasia, as a reality in some European countries.

In this edition of the Guide, Chapter 13 now considers aspects of pancreas, small bowel and uterus living donation, in addition to the psychosocial aspects of living donation. The new Chapter 14, Paediatric donation, elaborates all aspects of deceased donation in children, when death is determined either by neurologic or by circulatory criteria, and addresses the outcomes of organs obtained from paediatric donors. Chapter 15, Donation of vascularised composite allografts, has been revised and now includes uterus transplantation in detail.

Chapter 16, Biovigilance and surveillance, has been deeply revised to provide clear guidance on how to identify, report, assess and manage severe adverse reactions and events, in alignment with the *Guide to the quality and safety of tissues and cells for human application*. It is addressed not only to healthcare professionals reporting any SAREs, but also to healthcare authorities who need to put in place a biovigilance system. Chapter 17Chapter 17, Achieving and measuring quality in organ donation and transplantation, and Chapter 18, Measuring outcomes in transplantation, have been updated. Chapter 17 provides detailed principles of quality management for organ donation and procurement, as well as for transplantation activities. Chapter 18 reviews the factors to be considered when measuring outcomes in transplantation.

Finally, the new Chapter 19, Communication of

risk and shared decision-making, addresses consent for living organ donation and organ transplantation and provides guidance for crisis management and communication when facing a serious adverse reaction or event.

Expertise involved and acknowledgements

A dedicated working group including well-known experts nominated by the national Health Authorities of Council of Europe member states was convened for the elaboration of this Guide. This group was chaired by Beatriz Domínguez-Gil (Organización Nacional de Trasplantes, Spain) and Carl-Ludwig Fischer-Fröhlich (Deutsche Stiftung Organtransplantation, Germany). This expert group made exceptional contributions by sharing their expertise, reviewing the literature in their respective specialist areas and extracting and distilling knowledge from numerous international guidelines, collaborative projects and diverse publications and websites, with the aim of ensuring that all this up-to-date information is made available and accessible to professionals and regulators. Members of the group co-ordinated the preparation of each chapter and ensured access to the best expertise in each field by engaging additional external experts, who co-authored and contributed to the discussions on various parts of this Guide. The names of all the experts who participated in the elaboration of this Guide can be found in Appendix 33.

The final draft was submitted to a stakeholder consultation where Health Authorities, relevant professional associations and additional experts nominated by them carefully revised the text and provided comments and suggestions. During the consultation for this 8th edition, 301 comments were received; all of them were carefully analysed by the working group and 84 % of the comments led to changes in the final text. In some instances (7 %), comments were deemed relevant but required extensive research and/or discussion, so their inclusion was postponed to a future edition, and in 5 % of cases the comments did not require any changes to the text. Our gratitude is extended to all those individuals who provided extremely useful feedback during this stakeholder consultation.

Both the European Society for Organ Transplantation (ESOT) and CET should be thanked for sharing their expertise and knowledge and for enriching this 8th edition with the series of evidence-based reports previously described.

The drafting and publication of the 8th edition of the Guide was co-ordinated by Jaime Marco (Scientific Assistant) and Marta López Fraga (Scientific Officer in charge of the Council of Europe European Committee on Organ Transplantation [CD-P-TO]), with the assistance of Janet Latzel, Mar Lomero, Stéphanie Pierre-Charles, David Crowe and Gerard M.-F. Hill. The final result is this Guide, which constitutes a common European standard, based on the long-standing expertise and knowledge of the EDQM.

Last, but not least, we would like to honour all healthcare professionals who have been on the front lines against the pandemic. Their efforts, dedication and tireless work against Covid-19 have made them the true heroes of this health crisis. They have not only fought for our lives and those of our loved ones but also ensured that the gift of donation continued to save and improve lives through this unimaginable period.

Marta López Fraga
European Committee on Organ Transplantation (CD-P-TO)
Council of Europe

Chapter 1. Introduction

1.1. Scope and purpose of this Guide

Ever since the first successful kidney transplant was performed in 1954, organ transplantation has saved and improved the quality of life of thousands of patients. Today it is the best life-saving treatment for end-stage organ failure and is performed in 111 countries all over the world. According to the database of the Global Observatory on Donation and Transplantation (GODT), 153 863 solid-organ transplants (kidney, liver, heart, lung, pancreas, small bowel) were performed in 2019, of which 100 097 were kidney transplants, followed by 35 784 liver transplants [1]. However, it is estimated that this represents less than 10 % of global needs. Long periods on the waiting list for organs may result in patients dying or enduring a poor quality of life before transplantation. By the end of 2019, there were 92 574 patients waiting for a transplant in Europe, and 18 patients on the waiting list died every day because there was no organ available [2].

The field of organ donation and transplantation has been forced to evolve rapidly in order to cope with transplant needs, but this has come with inherent challenges. These include ensuring effective organisation, co-ordination and control of all relevant activities and services as well as the need for safeguards against exploitation and misuse [3]. In order to overcome such barriers and to facilitate access to safe and ethical transplantation therapy for all European citizens, the Council of Europe started to work in this area back in 1987. In 1999, a working group was set up to prepare a guide on the quality and safety standards that should apply to the donation, procurement and transplantation of human organs, tissues and cells in member states. The 1st edition of that Guide was published in 2002, and it has evolved very much since then.

This is the 8th edition of the *Guide to the quality and safety of organs for transplantation* of the Council of Europe. This Guide has two main objectives. Firstly, it aims to provide sound information and guidance for all professionals involved in donation and transplantation of human organs, to optimise the quality and minimise the risks of these complex procedures. All material of human origin carries risks that must be controlled by application of scrupulous criteria for donor evaluation and selection, and by comprehensive systems to assess quality. The idea is to help professionals on a practical level by providing easy-to-use information at the bedside that will help improve the rate of success of organ transplantation. Secondly, this Guide reflects ethical principles and guidelines to be considered for the donation and transplantation of human organs.

The field of organ donation and transplantation is now highly regulated in many countries. In the European Union (EU), Directive 2010/53/EU of the European Parliament and the Council provides the mandatory standards for quality and safety of human organs intended for transplantation, and Commission Implementing Directive 2012/25/EU lays down the information procedures for the exchange, between EU member states, of human organs intended for transplantation. Both directives should

already be transposed into the national legislations of the 27 EU member states. This Guide refers to those requirements where appropriate, providing technical examples of how they can be implemented, but goes beyond them to describe generally accepted good practice. Therefore, it will be useful as a source of practical information for those working within the EU legislative framework and for those working within national legal frameworks in all Council of Europe member states and non-member countries. In summary, this Guide is not intended to provide a common legal framework but aims at presenting technical guidance according to the best practices accepted at European level.

In this Guide the term 'Health Authority' is used throughout to refer to the body to which has been delegated the responsibility on a national or regional basis (or even sometimes at supranational level) by the government to ensure that organ donation and transplantation are appropriately promoted, regulated and monitored in the interests of patient safety and public transparency. Other terms – such as 'regulatory authority' and 'regulatory agency' or, in the EU, 'competent authority' and 'delegated body' – can be considered as equivalent to it.

This Guide is the result of the collective effort and expertise gathered by the members and observers of the European Committee of Experts on Organ Transplantation (CD-P-TO) through an *ad hoc* Organ Expert Group (see Appendices 33 and 34). Unless otherwise indicated, 'member states' means and applies to member states of the Council of Europe.

Appendix 1 spells out the abbreviations and acronyms used throughout this Guide and Appendix 2 is a glossary of key terms.

For matters dealing with the use of tissues and cells, and of blood or blood products, see the latest edition of the Council of Europe *Guide to the quality and safety of tissues and cells for human application* and the *Guide to the preparation, use and quality assurance of blood components* [4], respectively.

1.2. European Committee on Organ Transplantation, the European Directorate for the Quality of Medicines & HealthCare and the Council of Europe

The Council of Europe, based in Strasbourg (France), is an international organisation that promotes co-operation between all European countries in the areas of human rights, democracy, rule of law, culture and public health. After the 3rd Conference of European Health Ministers on the Ethical, Organisational and Legislative Aspects of Organ Transplantation [5] held in Paris in 1987, the Council of Europe Committee of Experts on the Organisational Aspects of Co-operation in Organ Transplantation (SP-CTO) was created. This committee consisted of experts in different aspects of transplantation: immunologists, surgeons, physicians, donor co-ordinators and representatives from organ-sharing and organ-procurement organisations. In 2007, the secretariat responsible for activities related to organs, tissues and cells was transferred to the European Directorate for the Quality of Medicines & HealthCare (EDQM) of the Council of Europe [6], and the newly appointed CD-P-TO took over as the steering committee [7]. This move to the EDQM facilitated closer collaboration and synergies with the EU and aimed, among other objectives, to avoid duplication of efforts.

It is under the mandate and aegis of the CD-P-TO committee that this Guide has been elaborated. Today, the CD-P-TO is composed of internationally recognised experts from Council of Europe member states, observer countries, the European Commission and the World Health Organization (WHO), with representatives from the Committee on Bioethics of the Council of Europe (DH-BIO) and several non-governmental organisations. The CD-P-TO actively promotes the non-commercialisation of human organs, the fight against organ trafficking and against trafficking with persons for the purpose of the removal of organs, the development of ethical, quality and safety standards in the field of transplantation of organs, tissues and cells, and the transfer of knowledge and expertise between member states and organisations.

1.3. General principles on donation and transplantation

1.3.1. Recent progress

Over the past 50 years, due to medical advances in the field and with the excellent results achieved in the transplantation of all types of human organs, organ transplantation has become a consolidated therapy. Kidney transplantation is the most cost-effective treatment for end-stage renal diseases. Compared to renal-replacement therapies with dialysis, kidney transplantation allows for a longer life span (on average, kidney transplant patients live 10–15 years longer than those on dialysis), improved quality of life, fewer medical complications (e.g. anaemia,

bone, heart and vascular disease related to dialysis therapy) and reduced costs for healthcare systems. For end-stage failure of organs such as liver, lung and heart, transplantation is the only available treatment.

Most European countries have increased their number of deceased organ donors since the 1990s, and in four of those countries the number annually is over 1 000 (see Figures 1.1 and 1.2). For kidneys, the number of living donors is also generally on the rise. However, waiting lists persist and, due to the chronic shortage of organs, some transplant clinicians are extremely selective about the patients they place on waiting lists.

The scarcity of organs to cope with the needs of transplantation has many intertwined causes, including: the increase in the number of indications for transplants; the failure to identify and refer possible organ donors; consent declined to proceed with organ recovery; and, more generally, limited institutional support for deceased donation in some countries and the way health and transplantation systems are organised and managed. While the issues concerned may be complex, there is one clear fact: that organ shortage is an increasingly acute problem in the context of an ageing population and the increased incidence of hypertension, diabetes and obesity – conditions that influence both the pool of potential donors and the number of patients waitlisted for a transplant.

In this context the need to tackle the problem of organ shortage has led to consideration of different strategies to increase organ availability, including living donation, donation after death determined by circulatory criteria (DCD), the use of organs from expanded-criteria donors and non-standard risk donors and the identification of donation opportunities beyond critical care units. All of these aspects are discussed at length in dedicated chapters of this Guide.

1.3.2. Risks and benefits of transplantation

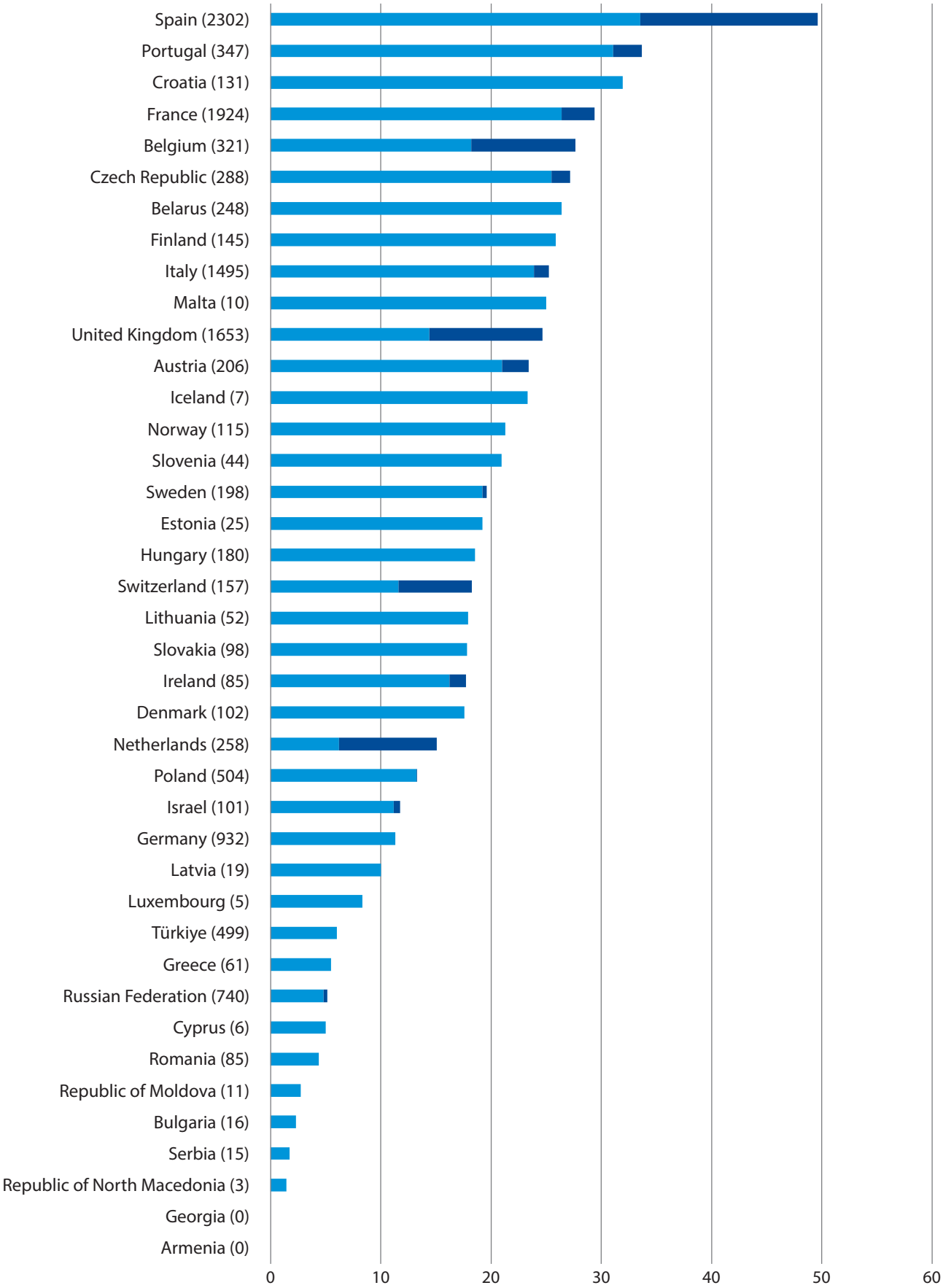
Transplantation is not without risks, and only organs procured under strict quality and safety parameters are likely to function properly and provide the best clinical outcomes for the recipients. Transplantation carries the risk of the operative procedure itself, of the lifelong immunosuppression that will be necessary and of disease transmission. The factors influencing the clinical outcomes of transplantation are complex: in particular, there is an interaction between two different biological systems: those of the donor and the recipient. Therefore, when assessing the risk of transplantation, both the donor and the recipient should be considered.

Risk evaluation of both donor and recipient factors has to be carried out on an individual, case-by-case basis. There may be factors that make a given organ from a donor absolutely unsuitable for a specific recipient, whereas the same organ could be effectively used, and indeed life-saving, for another recipient. It is the duty of the transplant team to carefully evaluate donor and recipient factors through an individual risk–benefit analysis. An individualised donor/organ profile should be produced for each patient enrolled on a transplant waiting list, weighing the risk of disease transmission or decreased quality of the transplanted organ against the risk of the recipient dying or deteriorating while on the waiting list. This approach facilitates the best use of all suitable organs. It is important to emphasise that the risks associated with transplantation can never be completely eliminated.

In the case of living donors, the short- and long-term outcomes should be assessed for the living donor, as well as for the recipient, to document benefit and harm. In both cases, the potential benefits of the transplant procedure should outweigh the risks. Donors must be carefully screened before donation; they must not be permitted to donate in clinically hopeless situations and must receive regular long-term follow-up care after donation. Transparent communication of these risks between all parties in the donation process is vitally important.

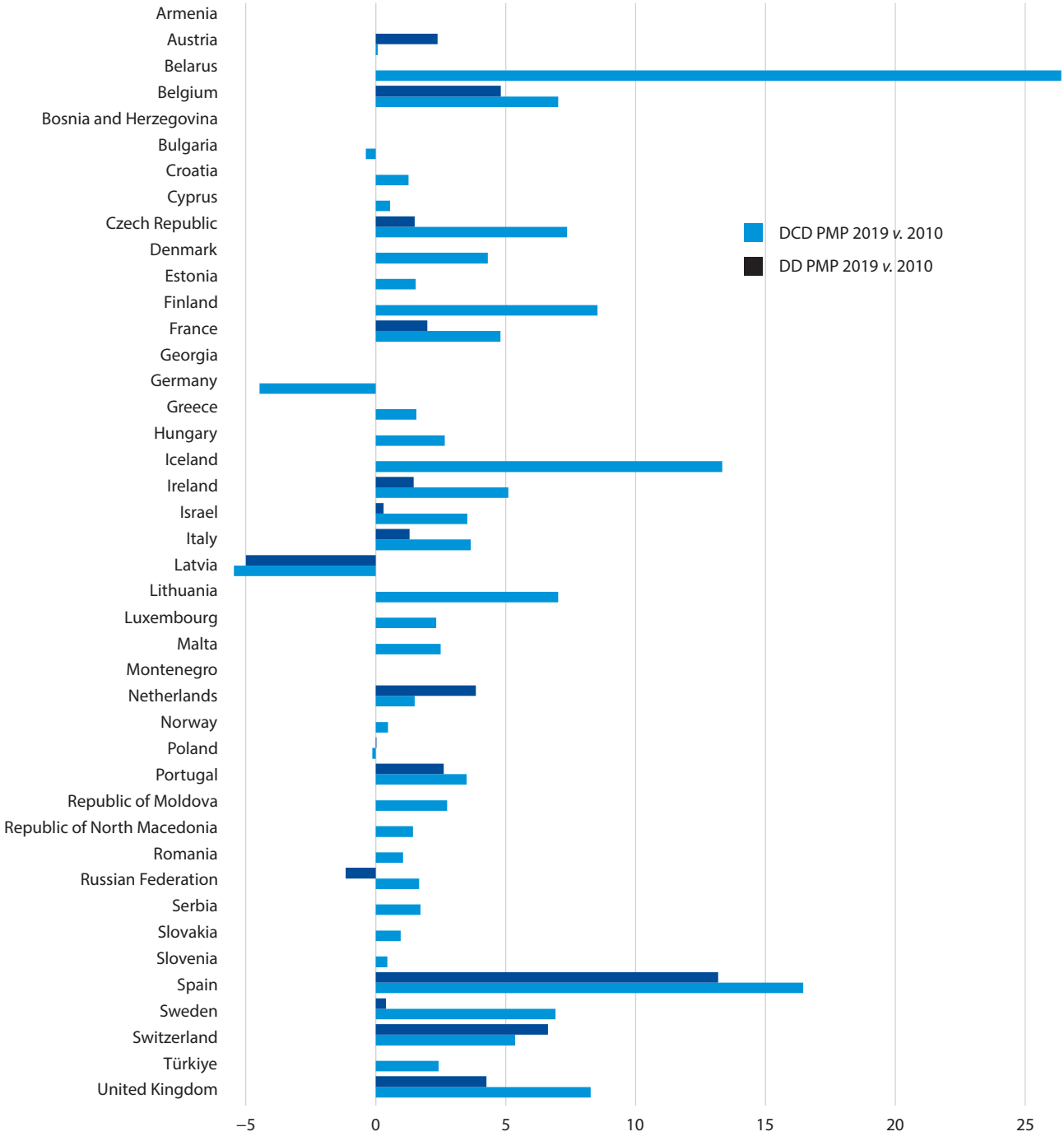
The transplantation of vascularised composite allografts (VCAs) is a treatment for complex tissue injuries and defects, and a growing field of activity in the past 15 years. Unlike most solid-organ transplantations, the transplantation of VCAs is not usually life-saving, and its primary aim is to improve a patient's quality of life. To date, primary applications of this type of transplantation have been of the hand and face (partial and full), although there are also reported cases of several other VCAs, including those of the larynx, knee, uterus or abdominal wall. VCAs are differentiated parts of the human body, containing skin, muscles, bones, tendons and vessels that require surgical connection of blood vessels and nerves for allograft function. Once transplanted, they maintain their structure, vascularisation and capacity to develop physiological functions at a significantly autonomous level. They are also subject to the same time constraints as organs because of their vulnerability to ischaemia, the absence of storage options and the need for immunosuppressive therapy. Therefore, VCAs are considered as organs [8].

Figure 1.1. **Deceased donation rates per million in Europe**



Source: *Newsletter Transplant*. Data from 2019.
DBD = donation after brain death; DCD = donation after circulatory death; pmp = per million population.
Data in parentheses: total number of deceased organ donors in 2019.

Figure 1.2. **Variation in deceased donation activities per million in Europe 2019 *v.* 2010**



Source: *Newsletter Transplant*.

DD: deceased donation (donation after brain death + donation after circulatory death); DCD: donation after circulatory death; pmp: per million population.

Any medical treatment, including any surgical procedure, normally requires the informed consent of the patient. In transplant medicine, informed consent concerning the quality of an organ to be transplanted and the risk of the individual procedure cannot be easily described in all details because of the limitations and problems outlined in the following chapters of this Guide. In comparison with other medical procedures, there are no valid scientific data about individual donor–recipient risk correlations available based on donor–recipient populations of sufficiently large size.

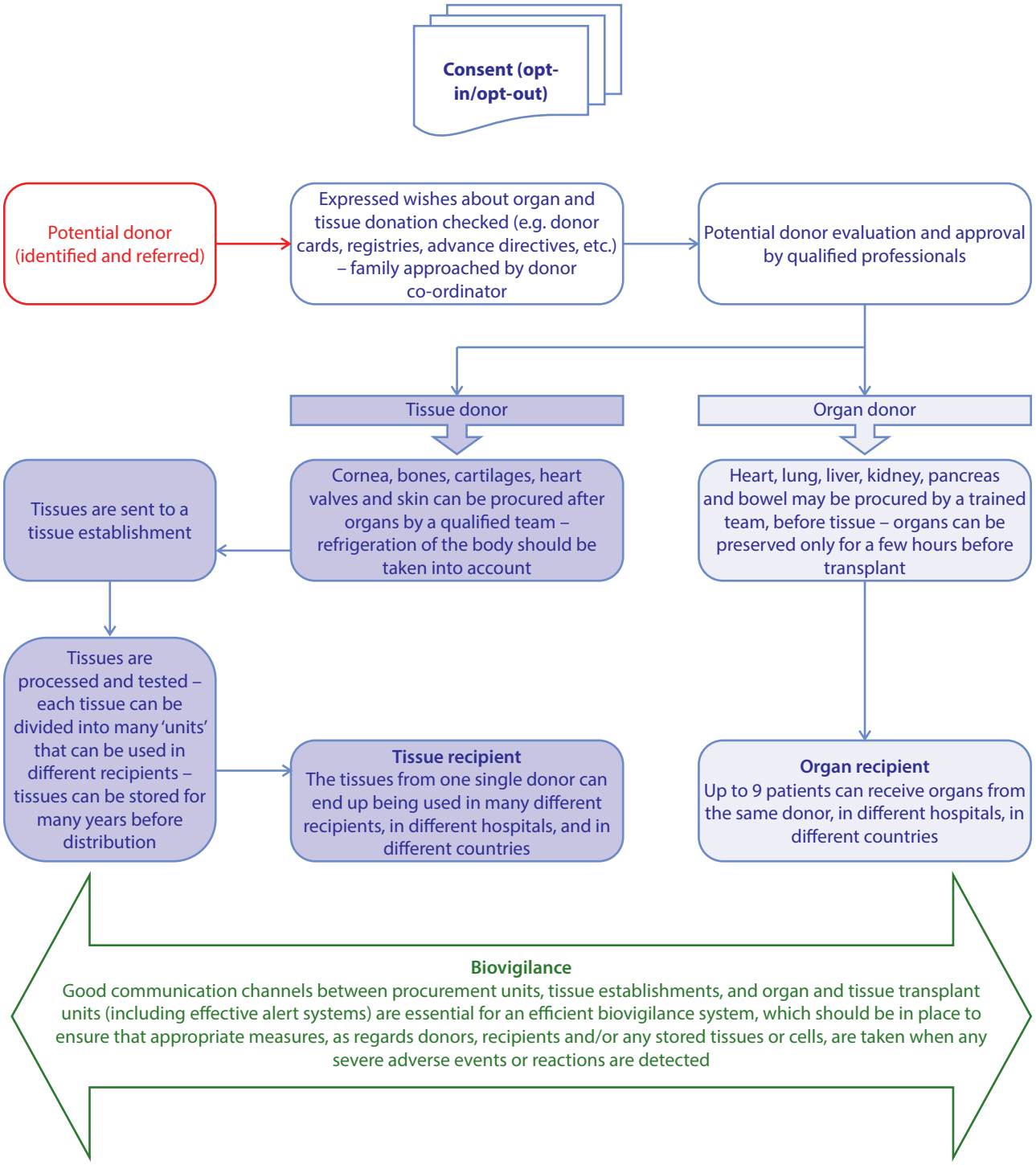
Patients, when registered on transplant waiting lists, should be informed of general risks about the surgical transplantation procedure, but also about the possibilities of disease transmission from donor to recipient. They should be advised that additional information or test results for a risk of disease transmission may become available only after transplantation. In this case, appropriate post-transplant testing,

prevention and/or therapy should be offered to mitigate the risk or the severity of disease transmission. Additionally, there are risks associated with a new outbreak of latent infectious diseases under immunosuppression, such as reactivation of *Cytomegalovirus*. Presentation of complications due to immunosuppressive therapy can increase, particularly if extended immunosuppressive protocols (using mono- or polyclonal antibodies as induction therapy) are used.

It is advisable to explain the options and potential risks associated with accepting – or not accepting – an organ from a non-standard-risk donor at the time of enrolling for organ transplantation. This discussion should also clarify that risk factors may be present, but not recognised, at the time of an organ offer and that additional data related to risk may be discovered after the transplant procedure.

The patient should be reassured that the physicians and all personnel involved in the process of organ donation and transplantation are working on

Figure 1.3. **Complex links between donors and recipients in the context of donation after death**



the basis of 'best knowledge' and will offer appropriate screening and treatment to mitigate any potential for disease transmission. Nevertheless, sometimes not all details of the medical history of a donor may be available because either the donor's family or the general practitioner in charge of a person's healthcare does not know all the data, for various reasons.

When performing a transplant, the specific, informed consent and the will of the recipient should be taken into account in the allocation procedure. However, the criteria under which a given recipient would/could accept an organ may change over time as a result of a deterioration in their clinical situation. As a consequence, regular re-evaluations of recipient willingness to accept non-standard-risk organ donors should be made, particularly when there are changes in an individual's clinical status. For example, a highly urgent heart recipient in an intensive care unit with only a few days or weeks of life expectancy might be willing to accept a much higher risk from a donor organ compared to a recipient in a stable condition.

Knowledge in the field of transplantation medicine has increased to an extremely high level in the past 20 years. Given the number of transplants performed worldwide and the few reported adverse incidents, the risk of transplantation might not be seen as too high. However, some decisions in transplantation medicine are based on clinical experience, in addition to a high level of common sense. Clinical experience is basically the only source of data, since randomised clinical trials are not always feasible.

Decisions concerning the risk of disease transmission from a donor to one or more recipients should be based on the best scientific knowledge, and the expected results of such decisions should be verified through post-transplant follow-up.

All patients (or parents/legal guardians of under-age patients) who are candidates for transplant waiting lists, or those changing their status on waiting lists, should know about these risks. While discussing all the risks related to donation and transplantation, society must keep in mind that not transplanting an organ into a waiting patient due to organ shortage is the biggest risk in transplantation medicine. Medical professionals must ensure that risk-avoiding behaviour – regardless of any excuse – causes organ wastage in this context.

1.3.3. Process of donation and transplantation of organs

Organ donation and transplantation continue to be fast-moving fields, requiring control of all the crucial technical activities and services that enable organs to be removed from one person and transferred to another person, including: identification, referral and maintenance of donors; procurement, transportation and preservation of organs; quality management; reimbursement of expenses and service charges; and safeguards against exploitation or misuse (e.g., formal requirements for consent from the potential donor before material may be taken).

The process of donation of organs from a deceased donor is, in many respects, quite different from the process in living donors. However, in all cases, a complex network of interactions underlies the many ways in which human organs, tissues and cells may be provided by one person for the benefit of others, and a complex chain of intermediaries (people and institutions) needs to be involved. Some of these complex links, using the example of a deceased donor of organs or tissue, are summarised in Figure 1.3.

The entire process may be viewed in terms of organisation and work flows. In the case of donation after death, transplantation can take place only if trained professionals are available to approach the family of the potential donor, if there is the necessary infrastructure and human resources to procure organs and tissues – including the steps of further processing – within a given timeframe, if appropriate services exist to transport organs and tissues in an adequate manner and if surgeons/physicians are available to participate in the transplantation procedure.

Similarly, to make living donation possible, professionals have to carefully select and evaluate potential donors, and ensure post-operative follow-up.

It is important to emphasise how policy surrounding donation must take into account the complex flows and multiple intermediaries involved in the process. Such policy awareness highlights the central part inevitably played in the donation and subsequent use of organs, tissues and cells by organisations and organisational structures.

The increasing possibility of using organs and many forms of human tissues to benefit others in medical treatment has brought increased pressure in member states to meet the transplantation needs of patients. There is a continual need to identify donors to maintain an adequate supply. Shortages of supply may affect particular subgroups of patients because of the need to match grafts according to immunological criteria or age. 'Demand' for organs and tissues is inherently variable since scientific developments may modify treatment options: the demand for treatment of end-stage organ failure by transplantation may increase, while the development of alternatives, such as prevention strategies for end-stage organ failure

(e.g. novel anti-viral drugs in hepatitis C) may reduce demand. Public expectations of what medical science can achieve may serve to put further upward pressure on demand.

Talking in terms of 'supply' and 'demand' may resonate with the experience of many professionals and patients (potential recipients), who are only too aware of the impact of any shortage in supply. This feature is exacerbated in situations in which the requirement for a high degree of matching or phenotypical similarity between donor and recipient calls for recruitment from ethnic minorities and international collaboration. However, at the same time, it may imply a lack of consideration of the human nature of the source of the organs. It is important always to emphasise when using these impersonal terms that behind 'supply' and 'demand' are individual people and their lives.

1.3.4. Organ allocation systems

Allocation of human organs for transplantation is a challenging phase in the process of organ donation and transplantation. Allocation criteria should be primarily based on medical criteria and be designed in accordance with ethical principles. In addition, a well-defined allocation system should take into account the self-sufficiency principle and the management of the transplantation waiting list.

All patients suffering from end-stage organ disease should be evaluated to assess their suitability for inclusion in the transplantation waiting list. Organs donated for transplantation from a deceased donor enter a common pool to be used according to need and should not be directed to a particular individual or specific group of individuals. Except in the case of direct living donations, organs must be allocated to patients only in line with transparent, objective and duly justified rules. Allocation rules, defined by appropriately constituted committees, should be equitable, externally justified, transparent and open to scrutiny. The persons or official bodies responsible for the allocation decision must be designated within this framework [9].

The main goal of organ allocation rules is to reach the optimal overall outcome after transplantation. Medical aspects should be balanced with the most relevant ethical principles, due to the scarce life-saving resource that human organs represent. In this regard, 'utility', 'justice' and 'autonomy of patients' are the guiding ethical principles to achieve an equitable outcome and fairness in allocation of organs used for transplantation [10]. The main consideration in the allocation process is minimising the number of patients dying while on the waiting list and transplanting patients before they become non-transplantable due to their illness progressing. Waiting-list priorities present an operational balance of ethical and moral principles that can sometimes come into conflict. While some waiting lists may favour priority to children, others prioritise those at highest risk of death over a certain period and others might favour those predicted to live longest after transplantation. Additional criteria should assure best possible match between donor and recipient for urgent and life-saving procedures and such criteria need special reviewing.

Existing practices and requirements may vary among countries or institutions and from one organ type to another. In practice, there are three main types of allocation system:

- patient-oriented
- centre-oriented
- mixed.

All three have advantages and disadvantages relating to patient outcomes and the influence on donation programmes. The centre-oriented system is very influential and stimulating for the local donor programme. On the other hand, the patient-oriented system offers more possibilities to reach the best match in line with all-important medical aspects.

Clearly defined access to the waiting list for organ transplantation is the fundamental prerequisite for organ allocation. Appropriate referral (of candidates for transplant and evaluation) is the responsibility of those caring for the patient with organ failure. Both geographic and socio-economic challenges may also impact referral of candidates for transplantation. Allocation practices based predominantly on waiting-list time need to be routinely examined to ensure that different practices do not discriminate against certain groups of patients.

Ethical principles, such as the concept of autonomy, and public opinion are important in allocation decisions. Support for this position arises from the fact that transplantation (a) is a public good, (b) depends on public funds for research and development, and (c) in most cases is paid for by public funds. Furthermore, transplantation depends on the willingness of the population to donate, and an unjust allocation system may adversely affect this decision [11]. The general public is capable of flexible and thoughtful approaches to transplant priorities, with their preferences being focused on maximisation of outcomes after transplantation, prioritising citizens or residents, keeping organs local and considering cost in allocation decisions [12].

Due to the complexity of the decision-making system, the responsibilities of the national or regional transplant organisation (NTO), or the health authorities, should be clearly established. NTOs are significantly involved in the system of setting up and supporting the entire donation process by co-ordinating activities at national policy level with hospital systems, as well as by implementing legal measures and organising organ and transplant team transport. The tasks of managing waiting lists, registries and statistics also predominantly fall within the purview of NTOs. In order to foster organ sharing, NTOs communicate with possible transplant centres and organ-sharing centres to facilitate the exchange of patient and donor data at national and international levels and, in some countries, they co-ordinate the entire organ procurement process.

While kidney transplants are now common practice in most countries, not all countries have yet developed capacities to transplant and/or procure all types of organ. To develop such programmes and to offer other options to their patients, as well as to avoid losing organs, many countries have engaged in international organ exchanges, via bilateral (between two countries or authorities) or multilateral agreements (e.g. in Europe: Eurotransplant, Scandiatransplant or the South Alliance for Transplantation). In the case of international organ exchange arrangements, procedures must also ensure justified and effective distribution across the participating countries in a manner that takes into account the solidarity principle within each country.

1.3.5. Health authorities and/or national transplant organisations

Transplantation is a complex process requiring a large number of functions to be managed effectively by health authorities. Optimising the outcome of organ transplantation entails a rules-based process that encompasses clinical interventions and procedures, from donor selection through to long-term follow-up of transplanted recipients. Ideally, these functions should all be the responsibility of a single public body, referred to as a national transplant organisation (NTO). However, a combination of local, regional, national and/or international bodies may work together to co-ordinate donation, allocation and/or transplantation, provided that the framework in place ensures accountability, co-operation and efficiency.

This Health Authority (or NTO) should be responsible for the authorisation (including accreditation, licensing and designation) of centres, along with the organisation and monitoring of organ, tissue and cell donation and transplantation, and it should have a statutory basis which clearly sets out its structure, powers and responsibilities.

According to Recommendation Rec (2006) 15 of the Council of Europe Committee of Ministers [13], health authorities should have competencies and mechanisms to organise and oversee the whole process of transplantation, including: public education on organ (and tissue) donation and procurement; transplantation; national transplant recipient waiting lists; organ (and tissue) allocation; organ (and tissue) transportation, including international exchanges; authorisation of organ procurement and transplant teams or institutions; traceability of organs and tissues; and monitoring of the outcomes of transplantation and donations from living donors. Other competencies may include research into transplantation and responsibility for identifying and reporting to the relevant authorities any breaches of the national transplantation law.

The essential functions of an NTO (with its advisory committees) include:

a. running a central office which is operational 24 h a day, 7 days a week, with which all donors have to be registered and which manages national or international organ allocation;
b. ensuring that all relevant donor data, including screening results, are collected and communicated to the recipient's transplant team;
c. managing specific national waiting lists for organs and, if applicable, for tissues, on the basis of agreed and transparent national admission criteria, containing sufficient up-to-date data on the recipient to ensure optimal matching;
d. ensuring that all donated organs are allocated to the most appropriate recipient in compliance with nationally agreed and transparent allocation rules, to ensure as far as possible equal access to transplantation for all patients who could benefit from a transplant;
e. ensuring that arrangements are in place for the safe and rapid transport of organs from the donor's hospital to the recipient's hospital;
f. ensuring the maintenance of a transplant database of all donors and recipients, including follow-up data on living donors and recipients, to ensure traceability and to audit the outcome of transplant programmes;
g. taking responsibility for running a transplant quality-assurance system consistent with internationally recognised standards;
h. providing accurate information to profes-

sionals on organ and tissue donation and the outcomes of transplantation as well as being responsible for professional education about transplantation and raising the awareness of the public about organ and tissue donation and transplantation;

i. ensuring complete transparency of national transplant procedures and processes in order to maintain or improve public and patient trust;

j. ensuring follow-up of each transplanted organ for proper biovigilance and analysis of quality of the donation–transplantation process, with adjustments to the state of the art if necessary;

k. taking up national/international responsibility for tissue donation and transplantation.

Additionally, the following functions should ideally be the responsibility of the NTO, or its advisory committees. Alternatively, they could be taken by other bodies in co-operation with the NTO. Directive 2010/53/EU requires EU member states to designate one or more competent authorities (and delegated bodies) to implement tasks that cover many of the functions listed here, and defines broadly their tasks and responsibilities:

a. the recruitment, training and appointment of donor co-ordinators in all major hospitals with a potential for deceased organ donation;

b. the co-ordination and management of donors and/or other transplant co-ordinators;

c. conducting a regional/national potential donor audit to assess the potential donor 'pool', evaluate effectiveness in the realisation of the donation process and identify areas for improvement;

d. managing national organ donor/non-donor registers (consent-to-donation registers), if applicable;

e. reviewing donor-screening methods and requirements to ensure compatibility with international standards and adapting them to any specific local requirements, if applicable;

f. determining specific information requirements for organ and tissue donors;

g. setting standards for donor management;

h. setting standards for organ-recovery procedures, in particular multi-organ procurement operations, in order to maximise organ quality and preservation;

i. organising and co-ordinating organ donation and procurement procedures;

j. setting standards for organ and tissue packaging, labelling and transportation;

k. organising the transport of organs and tissues from the donor's hospital to the recipient's hospital or tissue establishment;

l. setting criteria for the admission of patients to national organ- or tissue-specific waiting lists;

m. reviewing and analysing national transplant waiting lists, that is, waiting times according to demography, geography, clinical status etc., as a basis for recommending changes to allocation rules in order to ensure optimum allocation of organs;

n. managing and analysing transplant data through the donation process, including an analysis of allocation, to ensure that the rules are properly applied and to prevent organ trafficking;

o. offering organs to other NTOs if a compatible recipient is not available and/or on the basis of international co-operative agreements;

p. maintaining registers of all donors, including living donors, and all transplant recipients and/or designing and operating an integrated national transplant information system;

q. in cases where a disease is transmitted to a recipient, identifying all other recipients of organs or tissues from that same donor, and/or ensuring the disposal of any unused organs or tissues;

r. offering advice on the types of transplant that should be financially covered by national health systems and any that may be allowed in the private sector;

s. accrediting transplant teams and/or institutions allowed to perform organ transplants;

t. managing and overseeing haematopoietic progenitor cell transplants, including the importation of haematopoietic progenitor cells;

u. collecting data on outcomes and follow-up from transplant teams and units;

v. auditing transplant procedures and outcomes to allow constant improvements in the safety and quality of organ transplantation;

w. submitting outcome data to international transplant registers;

x. organising and managing public relations and communication strategies on national transplantation issues;

y. identifying and exposing possible cases of organ trafficking;

z. setting standards for the screening and selection of potential living donors;

aa. authorising living donor transplants.

In view of a potential conflict of interest, setting the criteria to determine death, either by neurologic or by circulatory criteria (if within the scope of national law), should not be the responsibility of the NTO but of a separate and independent body. It is mandatory that this independent body takes the responsibility to ensure that death can be certified properly without delay when the relevant criteria are fulfilled.

Member states wishing to collaborate within the framework of a supranational organisation should consider that the NTO remains responsible for deciding on the functions to be allocated to an international body.

1.3.6. The central role of the donor co-ordinator

As mentioned earlier, organ donation and transplantation is a complex process that requires various services and therefore requires effective organisation and co-ordination of healthcare professionals. In many member states, the training and employment of donor co-ordinators has increased the rate of donation of organs and tissues for transplantation, enhanced the efficiency of their procurement and improved the functioning of local and national transplant systems. Donor co-ordinators may also be given other names, such as transplant co-ordinators or key donation persons. In Europe, different organisational structures and professional backgrounds for donor co-ordinators exist.

Council of Europe Recommendation Rec (2004) 19 of the Committee of Ministers defines the recommended role and training of these professionals. Donor co-ordinators responsible for the identification of possible deceased donors should be appointed in every hospital with an intensive care unit. They should have appropriate training and experience, be independent of any transplant teams and have clearly defined responsibilities for the establishment, management and audit of a hospital-based system for donor identification and organ/tissue procurement. These professionals should be responsible not only for monitoring the donation and procurement process but also for identifying and implementing improvements.

These professionals should be properly accountable to senior management of the relevant health institution and to any regional transplant organisation or NTO. Donor co-ordinators may be supported by, or report to, other donor co-ordinators at regional or national level.

Donor co-ordinators should receive continuing professional training consistent with internationally recognised standards, to ensure best possible professional and ethical practices in organ donation and procurement. Member states should establish formal national or international training and accreditation programmes for donor co-ordination activities/donor co-ordinators.

Their clinical responsibilities may include not only organ, but also tissue donation. They should also manage, record and evaluate the living donor procedure with regard to transparency, free will and other legal and ethical considerations. Their professional activities should include:

a. detecting and identifying possible donors;
b. supporting other professionals involved in the donation process, when needed;
c. supervising donor maintenance, evaluation and testing in order to maintain good organ perfusion and to ensure the quality and safety of the organs and tissues for transplantation;
d. approaching the relatives of potential donors and obtaining consent to donation;
e. overseeing the entire administrative and legal process of donation, including obtaining court orders when required;
f. organising organ and/or tissue procurement and distribution, co-ordinating the necessary and available resources for their procurement (operating rooms, anaesthesia, nursing, surgical teams, etc.) and subsequent distribution and transport to their final destination;
g. referring any potential tissue donors to the tissue establishments in the area/region.

1.4. Ethical considerations

Human organs can be procured only from the body of a person – hence the ethical challenges associated with their use. This Guide describes the very different circumstances under which a person can donate. The donor may be living or deceased; in the latter situation, the determination of death may be done using neurologic or circulatory criteria. Whatever the case, handling and disposal of human organs must be carried out in a manner that shows respect for fundamental rights and for the human body.

Ethical standards of all aspects of organ, tissue and cell donation and transplantation have to conform to the Oviedo Convention on Human Rights and Biomedicine (1997) [14] and the Additional Protocol on transplantation of organs and tissues of human origin (2002) [15]. In addition, all EU member states must comply with the EU directives in the field (see §1.5.3). Other important guide-

lines to be respected from an ethical viewpoint are Resolution (1978) 29 of the Committee of Ministers on harmonisation of legislation of member states relating to removal, grafting and transplantation of human substances [16], the WHO guiding principles on human cell, tissue and organ transplantation [17], the Declaration of Istanbul on Organ Trafficking and Transplant Tourism [18, 19] and the Council of Europe Guide for the implementation of the principle of prohibition of financial gain with respect to the human body [20].

1.4.1. Consent

The Oviedo Convention states that an intervention in the health field may be carried out only after the person concerned has given free and informed consent to it [14]. This person must make a free choice in the absence of any undue influence and must be given appropriate information beforehand as to the intended use and nature of the intervention as well as its consequences and risks. The person concerned may freely withdraw consent at any time. In the case of organ donation after death, consent can be given by relatives who know or can infer the willingness of the deceased person to donate. Where the willingness of the deceased person is not known, relatives may give consent based on their own judgement.

The Additional Protocol to the Convention on Human Rights and Biomedicine concerning transplantation of organs and tissues of human origin expands these provisions further for the specific case of donation and transplantation [15]. These provisions, along with other relevant information in the case of *post mortem* donation, are explained further in detail in Chapter 4. Specific cases related to consent in DCD and living donation are outlined in Chapter 12 and Chapter 13, respectively.

The 'dead-donor rule' (which states that patients must be declared dead before procurement of any vital organs or tissues for transplantation) must be strictly respected [21]. Organs must not be removed from the body of a deceased person unless the death of this person has been certified in accordance with the national law and consent or authorisation has been obtained. The procurement must not be carried out if the deceased person had objected to it.

Finally, it is crucial to emphasise the importance of consent in creating and maintaining the trust of the general public in health professionals and the healthcare system as a whole. Medical mistrust, or distrust of the healthcare system, is one of the reasons why people are reluctant to donate organs. This may be associated with concerns about consent in that the terms of the consent may be abused (for example, by using the donated material in a manner which is not in accordance with consent) or that additional material may be taken without explicit consent. Honesty and trust are central in both professional and personal relationships when donation of organs or tissues or cells takes place. Therefore, it is of vital importance that the limits of the consent are clearly established, explicit and scrupulously respected.

The recipient and, as necessary, the person or official body providing authorisation for the transplant, must be given appropriate information beforehand as to the purpose and nature of the procedure, and its consequences and risks, as well as on the alternatives to the intervention.

In summary, all donation and transplantation programmes are dependent upon goodwill and voluntary donation. It is therefore important that public confidence is maintained by standards of good practice. By engaging donor trust and commitment through obtaining consent, the risk of nefarious trading and potential physical harm from the use of organs will be reduced.

1.4.2. Conflicts of interest

To avoid any potential conflicts of interest, doctors certifying the death of a person must not be involved in the allocation procedure or be the same doctors who participate directly in the procurement of organs or tissues from the deceased person, or in subsequent transplantation procedures, or have responsibilities for the care of the potential organ or tissue recipients.

Health authorities will set out the legal standards for determining that death has occurred and specify how the criteria and process for determining death will be formulated and applied.

1.4.3. Financial aspects of donation and transplantation

Discussions around how to increase the supply of human organs often focus on questions of donor motivation, i.e. how individuals may best be encouraged to donate. Nevertheless, it is essential to recall the Oviedo Convention which, in Article 21, clearly states that the human body and its parts must not, as such, give rise to financial gain [14, 22]. This stipulation is reiterated in the Additional Protocol to that Convention, in its Article 21 [15], and has resulted in the publication by the Council of Europe of a guide to facilitate its implementation [20]. This guide underlines that the prohibition of financial gain does not

prevent living donors from being compensated for loss of earnings and the reimbursement of medical expenses, or from being compensated for unjustified damage resulting from the removal of organs, tissues or cells.

The Council of Europe Convention against Trafficking in Human Organs [23] clearly identifies distinct activities that constitute 'trafficking in human organs', which ratifying states are obliged to criminalise. The central concept is 'the illicit removal of organs', which includes removal where a living donor (or a third party) has been offered or received a financial gain or comparable advantage, or removal from a deceased donor where a third party has been offered or received a financial gain or comparable advantage.

These provisions do not prevent payments that do not constitute a financial gain or a comparable advantage, in particular:

a. compensation of living donors for loss of earnings and any other justifiable expenses caused by the removal or by the related medical examinations;
b. payment of a justifiable fee for legitimate medical or related technical services rendered in connection with transplantation;
c. compensation in case of undue damage resulting from the removal of organs from living persons.

In the donation of any organ, removal of barriers to donate must not render a decision to donate non-altruistic. Initiatives that reduce the barriers to donation should only facilitate an action that the individual was already inclined to take by concern for the welfare of the recipient. In this sense, the Nuffield Council on Bioethics suggests distinguishing between two types of intervention, both of which aim at increasing donation by changing its costs and benefits [21]. The first type is 'altruist-focused interventions', which typically involve removal of various disincentives to act and, in doing so, remove countervailing concerns that may hinder potential donors from acting on their altruistic motivations. For the purpose of this Guide, we will call these interventions 'compensation'. The second type is 'non-altruist-focused interventions', which are targeted at persons who have no strong motivation to help others through donation of their bodily material, but who would be disposed to donate if provided with different reasons for action, perhaps in the form of a payment or incentive going well beyond the reimbursement of expenses. These incentives are particularly worrisome as they may change the donor's perception of the relative risks and benefits of a donation that is not free of potential health hazards and psychological consequences, and such incentives will target the impoverished and vulnerable.

In summary, voluntary unpaid donation must continue to have a central role in the donation process of any organ. Compensation to donors should be strictly limited to making good the expenses and loss of income related to the donation and should not act as an incentive or inducement (either direct or indirect).

Physicians and other health professionals must not engage in transplantation procedures, and health insurers or other finance providers should not cover such procedures, if the organs concerned have been obtained through exploitation or coercion of, or payment to, the donor or the next of kin of a deceased donor.

Promotion of altruistic donation of human organs by means of advertisement or public appeal may be undertaken in accordance with domestic regulations. However, advertising the need for, or the availability of, organs with a view to offering or seeking financial gain or comparable advantage for the donor him/herself or a third party (e.g. the next of kin of the deceased organ donor) must be prohibited. Brokering that involves payment to such individuals or to third parties must also be prohibited.

1.4.4. Equal access to transplantation

Healthcare in general is a human right because it secures and protects access of people to the normal range of opportunities and because it allows people to thrive. Given the importance of health for general well-being, every person, regardless of their income or financial means, should have access to good healthcare.

The demand for human organs in many instances exceeds their availability. Significant practical and ethical questions regarding efficiency and fairness arise as to how to distribute these limited resources. Article 3 of the Additional Protocol to the Convention on Human Rights and Biomedicine concerning transplantation of organs and tissues of human origin states that transplantation systems must exist to provide equity in access to transplantation services for patients.

1.4.5. Equity in donation

Individual motivation and choice is only one part of the donation picture; the central role of organisations, organisational procedures and professionals

in facilitating donation should not be underestimated, nor indeed the importance of trust in these systems. An example of the organisational aspect is that, whenever a person dies in circumstances where donation is a possibility, this possibility should be raised.

The role of the state with respect to donation should be understood as one of stewardship: that is, actively promoting measures that will improve general health (thereby reducing the demand for some forms of bodily material) and facilitating donation [21]. Such a stewardship role should extend to taking action to remove inequalities that affect disadvantaged groups or individuals with respect to donation. Equity in donation refers to the absence of systematic disparities in the burden of donation between social groups who have different levels of underlying social advantage or disadvantage (i.e. different positions in a social hierarchy). Systemic inequities in donation would put groups of people who are already socially disadvantaged (e.g. by virtue of being poor, female and/or members of a disenfranchised racial, ethnic or religious group) at further disadvantage with respect to their health.

As discussed above, introduction of financial incentives for donation renders certain social groups particularly susceptible to disparities based on social and economic status.

Safeguards must be in place to guarantee that all living donors, regardless of their origin, receive similar care and follow-up. To prevent the abuse of donors coming from abroad, clear traceability arrangements must be in place to ensure that an initial evaluation of the donor has been undertaken by the referring hospital, that free and specific consent to the donation has been given and that long-term follow-up care can be provided. [22]

1.4.6. Anonymity

The identity of the donor and recipient should (except in the case of living donation between persons having a close personal relationship) remain strictly confidential. Such precautions will prevent abuse and protect the families of donors and recipients from feelings of anxiety associated with emotional involvement, obligation to return favours or guilt.

1.4.7. Transparency and protection of personal rights

The organisation and realisation of donation and transplantation activities, as well as their clinical results, must be transparent and open to scrutiny, while ensuring that the personal anonymity and privacy of donors and recipients is always protected (if relevant).

Transparency can be achieved by maintaining public access to regularly updated comprehensive data on processes (in particular, allocation), transplant activities and outcomes for both recipients and living donors, as well as data on organisation, budgets and funding. Such transparency is not inconsistent with shielding (from public access) information that could identify individual donors or recipients, while still respecting the requirement of traceability. The objective of the system should be not only to maximise the availability of data for scholarly study and governmental oversight but also to identify risks (and facilitate their mitigation) to minimise harm to donors and recipients.

1.5. Recommendations and regulations in the field

1.5.1. Council of Europe

Within the framework principle of sharing knowledge through international co-operation, the Council of Europe has established widely recognised recommendations and resolutions in the field of transplantation, covering the ethical, social, scientific and training aspects of the donation and transplantation of organs, tissues and cells [24]. Whereas agreements and conventions are binding on the states that ratify them, resolutions and recommendations are policy statements to governments that propose a common course of action to be followed.

The Council of Europe Convention for the Protection of Human Rights and Fundamental Freedoms (European Treaty Series No. 5) [25] is an international treaty to protect human rights and fundamental freedoms in Europe. It was drafted in 1950 by the then newly formed Council of Europe and entered into force on 3 September 1953.

The European Agreement on the Exchange of Therapeutic Substances of Human Origin (European Treaty Series No. 26) [26], signed in Paris on 15 December 1958, aims to provide mutual assistance with respect to the supply of therapeutic substances of human origin.

The European Agreement on the Exchange of Tissue-Typing Reagents (European Treaty Series No. 84) [27], signed in Strasbourg on 17 September 1974, laid the groundwork for the development of mutual assistance in the supply of tissue-typing reagents and establishment of joint rules between signatory parties.

At its 14th meeting (Rome, 9-10 October 2014) the CD-P-TO carefully examined this treaty and decided that, considering the state-of-the-art advances in tissue-typing, this treaty should be declared inactive without further need for promotion or monitoring. The Additional Protocol (European Treaty Series No. 89) [28], opened for signature on 24 June 1976 and entering into force on 23 April 1977, provided for the accession of the European Community (now the EU) to this agreement.

The Oviedo Convention for the Protection of Human Rights and Dignity of the Human Being with regard to the Application of Biology and Medicine: Convention on Human Rights and Biomedicine (European Treaty Series No. 164) [14] was opened for signature on 4 April 1997 and came into force on 1 December 1999. It is the first legally binding international text designed to preserve human dignity, fundamental rights and freedoms, through a series of principles guarding against the misuse of biological and medical applications. The Convention is inspired by the principle of the primacy of human beings over the sole interest of science or society. It lays down a series of principles applying to medical practice as well as biomedical research, organ transplantation and genetics. The Convention includes the principle of consent, non-discrimination on the basis of genetic characteristics, and protection of private life and access to information. The Convention specifically prohibits financial gain arising from the body and its parts, as such.

This latter Convention was extended further by an Additional Protocol to the Convention on Human Rights and Biomedicine concerning transplantation of organs and tissues of human origin (European Treaty Series No. 186) [15], which was opened for signature on 24 January 2002 in Strasbourg and came into force on 1 May 2006. It aims to protect the dignity and identity of everyone and to guarantee, without discrimination, respect for their integrity and other rights and fundamental freedoms with regard to transplantation of organs and tissues of human origin, thereby establishing principles for the protection of donors and recipients.

The Council of Europe Convention on Action against Trafficking in Human Beings, with its Explanatory Report (European Treaty Series No. 197) [29], which was opened for signature in Warsaw on 16 May 2005 and came into force on 1 February 2008, addresses the trafficking of human beings for the purpose of organ removal.

The Joint Council of Europe/United Nations Study on trafficking in organs, tissues and cells and trafficking in human beings for the purpose of the removal of organs [3], presented at the United Nations headquarters in New York on 13 October 2009, focuses on trafficking in organs, tissues and cells for the purpose of transplantation. The Joint Study made evident that existing criminal-law instruments dealing exclusively with trafficking in human beings (including for the purpose of organ removal) left loopholes that allowed several unethical transplantation-related activities to persist. This is why the Council of Europe decided to undertake the task of drafting a new international legally binding instrument against trafficking in human organs. The resulting Council of Europe Convention against Trafficking in Human Organs [23] and its Explanatory Report [30], which opened for signature in Santiago de Compostela on 25 March 2015, identified distinct activities that constitute 'trafficking in human organs'. The central concept is 'the illicit removal of organs', which consists of removal without the free, informed and specific consent of a living donor; removal from a deceased donor other than as authorised under domestic law; removal when, in exchange, a living donor (or a third party) has been offered or received a financial gain or comparable advantage; or removal from a deceased donor when a third party has been offered or received a financial gain or comparable advantage.

The document Organ shortage: current status and strategies for the improvement of organ donation – a European consensus document (2003) [31] aims to provide a step-by-step guide to the most effective ways of procuring the maximum number of high-quality organs for transplantation from deceased donors, based on an analysis of the scientific data available and relevant international experience.

Other major Council of Europe resolutions and recommendations [32] in the field of organ donation and transplantation include:

- Resolution CM/Res (78) 29 on harmonisation of legislation of member states relating to removal, grafting and transplantation of human substances [16], recommending the governments of member states to conform their laws to a set of rules annexed to this resolution or to adopt provisions conforming to these rules when introducing new legislation.
- Recommendation No. R (97) 15 of the Committee of Ministers to member states on xenotransplantation [33], recommending governments of member states to establish a mechanism for the registration and regulation of xenotransplantation with a view to minimising the risk of transmission of known or unknown

diseases and infections to either human or animal populations.

- Recommendation No. R (97) 16 of the Committee of Ministers to member states on liver transplantation from living related donors [34], providing rules and guidelines for carrying out transplantations using livers derived from living donors related to the recipients of those organs.
- Recommendation Rec (2001) 5 of the Committee of Ministers to member states on the management of organ transplant waiting lists [35], providing rules and guidelines for the creation, management and enrolment of patients in organ transplant waiting lists.
- Recommendation Rec (2003) 10 of the Committee of Ministers to member states on xenotransplantation [36] and its Explanatory Memorandum [37], providing principles and guidelines for governments to set up their own legislation and practice in the field of xenotransplantation, with a view to minimising the risk of transmission of known or unknown diseases and infections to populations.
- Recommendation Rec (2003) 12 of the Committee of Ministers to member states on organ donor registers [38], providing rules and guidelines for the creation, purpose, management, characteristics and enrolment of persons in organ donor registers.
- Recommendation Rec (2004) 7 of the Committee of Ministers to member states on organ trafficking [39], providing a list of requirements to protect the dignity and identity of all persons and to guarantee without discrimination their fundamental rights and freedoms with regard to organ, tissue and cell donation (both living and deceased) and transplantation.
- Recommendation Rec (2004) 19 of the Committee of Ministers to member states on criteria for the authorisation of organ transplantation facilities [40], providing guidelines to governments to ensure they provide high-quality transplant services for the benefit of their citizens.
- Recommendation Rec (2005) 11 of the Committee of Ministers to member states on the role and training of professionals responsible for organ donation (transplant donor co-ordinators) [41], providing guidelines and recommendations to governments of member states as regards the role, functions, responsibilities and training of the donor co-ordinators who should be appointed in every hospital with an intensive care unit.
- Recommendation Rec (2006) 15 of the Committee of Ministers to member states on the background, functions and responsibilities of an NTO [13], recommending governments of member states to set up comprehensive national transplantation systems with competencies and mechanisms to organise and oversee the entire process of transplantation, including: public education on transplantation; organ (and tissue/cell) donation and recovery; national transplant recipient waiting lists; organ (and tissue/cell) allocation; organ (and tissue/cell) transportation, including international exchanges; authorisation of organ transplant teams or institutions; the traceability of organs and tissues; and monitoring of the outcomes of transplantation and donations from living donors. Other NTO competencies may include research into transplantation and responsibility for identifying and reporting to the relevant authorities any breaches of national transplantation law.
- Recommendation Rec (2006) 16 of the Committee of Ministers to member states on quality improvement programmes for organ donation [42], recommending that the governments of member states take all necessary measures to ensure that quality improvement programmes for organ donation are put in place in every hospital where there is potential for organ donation, and providing guidelines for their creation, implementation and management.
- Resolution CM/Res (2008) 4 on adult-to-adult living donor liver transplantation [43], recommending that member states instruct the organisation responsible for accrediting transplantation programmes and regulating the allocation of organs to explicitly address the issue of adult-to-adult living donor liver transplantation and to establish accredited transplantation programmes for the performance of this type of transplantation, in compliance with strict quality, safety and ethical parameters.
- Resolution CM/Res (2008) 6 on transplantation of kidneys from living donors who are not genetically related to the recipient [44] provides general principles and measures to be taken into account when establishing regulations and procedures relating to the donation of a kidney for transplantation by a living donor not genetically linked to the recipient.
- Resolution CM/Res (2013) 55 on establishing

procedures for the collection and dissemination of data on transplant activities outside a domestic transplantation system [45], recommends member states to adopt and implement appropriate tools for data collection on illicit transplantation activities.

- Resolution CM/Res (2013) 56 on the development and optimisation of live kidney donation programmes [46] and its Explanatory Memorandum [47] recommend member states to foster programmes for kidney donation from live donors based on recognised ethical and professional standards.
- Resolution CM/Res (2015) 10 on the role and training of critical care professionals in deceased donation [48] recommends member states to provide a clear legal and ethical framework that will: guide healthcare professionals caring for potential organ donors; help ensure that professionals working in intensive care units and emergency departments receive continuous training from the outset of their clinical practice; encourage hospitals to incorporate organ donation as a routine activity in intensive care units and emergency care departments by appointing designated professionals in these areas where there is a potential for organ donation; and support the development of scientific and health services research in the field of donation after death.
- Resolution CM/Res (2015) 11 on establishing harmonised national living donor registries with a view to facilitating international data sharing [49] sets out the general guidelines for the construction of such national/international registries. In addition, the Explanatory Memorandum [50] accompanying this resolution provides a detailed list of the parameters intended for inclusion in any national living donor registry, defining a mandatory data set and an expanded set of variables, as well as those to be included in a 'Registry of registries' aimed at international data sharing.
- Resolution CM/Res (2017) 1 on principles for the selection, evaluation, donation and follow-up of non-resident living organ donors [22], elaborated by the European Committee on Organ Transplantation (CD-P-TO). It is aimed at protecting non-resident living donors who, for a number of reasons – economic, emotional, cultural or physical – may be particularly vulnerable, and whose post-donation care and follow-up may be difficult to guarantee.
- Resolution CM/Res (2017) 2, on establishing procedures for the management of patients having received an organ transplant abroad upon return to their home country to receive follow-up care [51], aims to protect all patients who have received an organ transplant, regardless of the circumstances in which it was obtained, and it also aims to safeguard public health by recommending that all patients undergoing organ transplantation are systematically registered in national transplant records.
- Recommendation CM/Rec (2020) 4 of the Committee of Ministers to member States on the quality and safety of organs for transplantation [52] recommends member States to ensure that quality and safety standards for organ donation and transplantation are set in place in accordance with the guidelines set out in the *Guide to the quality and safety of organs for transplantation*.
- Recommendation CM/Rec (2020) 5 of the Committee of Ministers to member States on the quality and safety of tissues and cells for human application [53] recommends member States to ensure that quality and safety standards for the donation, preparation and clinical application of tissues and cells are carried out in accordance with the guidelines set out in the *Guide to the quality and safety of tissues and cells for human application*.
- Recommendation CM/Rec (2020) 6 of the Committee of Ministers to member States on establishing harmonised measures for the protection of haematopoietic progenitor cell donors [54] recommends member States to establish haematopoietic progenitor cell donor protection measures which should be identical irrespective of the type of donor (related or unrelated, adult or minor). In its appendix 1 it includes recommendations for the medical suitability assessment and eligibility criteria for haematopoietic progenitor cell donors.

Monitoring of practices in member states has become an evident need for the sake of transparency and international benchmarking. Keeping this goal in mind, since 1996 the EDQM/Council of Europe has published the *Newsletter Transplant* [2], which is co-ordinated by the Organización Nacional de Trasplantes (ONT) in Spain. This publication summarises comprehensive data provided by national focal points, designated by governments, on donation and transplantation activities, management of waiting lists, organ-donation refusals and authorised centres for transplantation activities. *Newsletter Transplant*

provides information from ≈ 70 countries, including Council of Europe member states, observer countries and observer networks (e.g. the Iberoamerican Donation and Network Council on Organ Donation and Transplantation, the Mediterranean Network). The *Newsletter Transplant* database is connected with other international projects on data collection (e.g. the WHO Global Observatory on Organ Donation and Transplantation, the Eurocet database of the European Registry for Organs, Tissues and Cells) to avoid duplication of efforts. *Newsletter Transplant* has evolved into a unique official source of information that continues to inspire policies and strategic plans worldwide.

The Council of Europe also produces other guidelines, including this *Guide to the quality and safety of organs for transplantation*, the *Guide to the quality and safety of tissues and cells for human application* and the *Guide to the preparation, use and quality assurance of blood components* [4].

1.5.2. World Health Organization and United Nations

In 1987, the 40th World Health Assembly, concerned about the trade for profit in human organs, initiated the preparation of the first WHO Guiding principles on transplantation, endorsed by the Assembly in 1991 through Resolution WHA44.25 [55]. These guiding principles have greatly influenced professional codes and practices, as well as legislation, around the world for almost two decades. After a consultation that took several years, on 21 May 2010 the 63rd World Health Assembly adopted Resolution WHA63.22 [56], which endorsed the updated WHO Guiding principles on human cell, tissue and organ transplantation [17] and called on WHO member states to implement these guiding principles, promote voluntary and unremunerated donation, oppose trafficking, and promote transparent and equitable allocation. It also urged its members to strengthen oversight, to collect and publish activity data, including adverse events and reactions, and to implement globally standardised coding. These guidelines are intended to provide an orderly, ethical and acceptable framework for the acquisition and transplantation of human cells, tissues and organs for therapeutic purposes.

The World Health Assembly adopted Resolution WHA57.18 [57] in 2004, which urged WHO member states 'to take measures to protect the poorest and vulnerable groups from transplant tourism and the sale of tissues and organs, including attention to the wider problem of international trafficking in human tissues and organs'. Robust bi-directional donor–recipient traceability is a prerequisite to achieving effective vigilance and surveillance worldwide. For this reason, Resolution WHA63.22 [56] also urged WHO member states to collaborate in collecting data (including adverse events and reactions) in addition to implementation of globally consistent coding systems. The Notify project was a specific follow-up action that was led by the WHO to promote the sharing of information on adverse incidents for improving safety and efficacy [58].

As a result of resolutions WHA57.18 and WHA63.22 (which requested that global data on the practice, safety, quality, efficacy and epidemiology of transplantations be collected in the WHO member states that have transplantation programmes), an international watchdog on transplantation was set up as a collaborative initiative between the Spanish ONT and WHO, and was termed the Global Observatory on Donation and Transplantation [1]. The universal availability of these data is recognised as a prerequisite for global improvements in demonstrating transparency, equity and compliance, and for monitoring national systems. In addition, the data provided also help to give an overview of the legal and organisational aspects in very different settings and countries, which enables the regulating bodies to monitor transplantation activities.

The WHO has also published two aides-mémoire specifically on the donation and transplantation of tissues and cells [59, 60].

In recent years, the WHO has been promoting use of the term 'medical products of human origin' (MPHO). This category includes blood, organs, tissues, bone marrow, cord blood, reproductive cells and milk derived from humans for therapeutic use. Use of these MPHO, obtained from living and deceased donors, entails practical, scientific and ethical considerations.

In 2018, the UN General Assembly adopted Resolution 73/189 on strengthening and promoting effective measures and international co-operation on organ donation and transplantation to prevent and combat trafficking in persons for the purpose of organ removal and trafficking in human organs [61], urging member States to prevent and combat trafficking in persons for the purpose of organ removal and trafficking in human organs, to ratify the United Nations Convention against Transnational Organized Crime and the Protocol to prevent, Suppress and Punish Trafficking in Persons, especially Women and Children, and to consider adopting measures related to organ transplantation, in accordance with the fundamental principles of their legal systems

and national legislation and in line with the World Health Organization guiding principles on human cell, tissue and organ transplantation.

1.5.3. European Union

The EU is an economic and political union of 27 member states that are located in Europe, together with candidate countries and associated countries. The EU operates through a system of European institutions (including the European Commission, the Council of the European Union and the European Parliament) and intergovernmental decisions negotiated by the member states. In the field of organs, but also tissues and cells and blood, the Council of Europe (EDQM) and the European Commission [62] have a standing collaboration aimed, among other objectives, at avoiding duplication of efforts and at increasing the dissemination and exchange of knowledge and expertise.

Acknowledging that organ transplantation is an expanding medical field that offers important opportunities for the treatment of organ failure, the EU aims for a common approach to regulation across Europe.

Article 168 of the Treaty on the Functioning of the European Union [63] (previously Article 152 of the Treaty of Amsterdam) gives the EU a mandate to establish high quality and safety standards for substances of human origin, such as blood, organs, tissues and cells. Directive 2010/53/EU of the European Parliament on standards of quality and safety of human organs intended for transplantation [64] was adopted on 7 July 2010 (see Corrigendum [65] to the Directive). This directive clearly states that 'Member States shall ensure that donations of organs from deceased and living donors are voluntary and unpaid'. It provides for the appointment of Competent Authorities in all member states, for the authorisation of procurement and transplantation centres and activities, for the establishment of traceability systems and for the reporting of serious adverse events and reactions. Moreover, the directive sets requirements for the safe transportation of organs and for the characterisation of every donor and organ. More specifically, for human organs exchanged between EU member states for transplantation purposes, Commission Implementing Directive 2012/25/EU was adopted on 9 October 2012 to lay down information procedures [66]. This directive refers only to organs exchanged across borders and does not cover patients travelling to another country for transplantation purposes, which should only be done in the strict framework of bilateral or multilateral co-operation agreements between member states and/or organ exchange organisations.

The EU [67] has addressed three different challenges in the field of organ donation and transplantation in the European setting: increasing organ availability, enhancing quality and safety, and making transplantation systems more accessible. It has done this by supporting its member states in their efforts to implement Directive 2010/53/EU and the Commission's Action Plan on Organ Donation and Transplantation (2009–2015): Strengthened Co-operation between Member States [68]. To mark the mid-term period of the action plan, EU member states adopted in December 2012 the conclusions of the Council of the European Union on organ donation and transplantation [69], recalling the main principles and objectives. In addition, based on the Actor Study [70], the Commission issued a document where efforts at national and European levels were mapped [71]. A study on the uptake and impact of the EU action plan on organ donation and transplantation (2009–15) in the EU member states, the Factor study [72], was published in 2018, concluding that the action plan has mainly facilitated that countries work together; resulting in an improvement of the transplant system and it recommends that this co-operation should continue.

Aimed at improving co-operation between EU member states in this field, several projects have been funded by the European Commission under the Research Programme – 6th and 7th Framework Programmes, Horizon 2020 – and under the (Public) Health Programmes run by the Consumers, Health, Agriculture and Food Executive. Some of these projects [73] are:

- Alliance-O [74] (European Group for Co-ordination of National Research Programmes on Organ Donation and Transplantation, 2004–07, FP6): the objective of this project was to ensure co-ordination of national research programmes in the field of organ transplantation for the seven countries involved.
- Dopki [75] (Improving Knowledge and Practices in Organ Donation, 2006-08, FP6): this project sought to improve organ donation rates. Researchers developed a methodology to determine the potential for donation and its likely outcome. The project produced indicators to be used to benchmark organ donation potential; it also defined risk levels in the donor evaluation process, produced actions to improve organ donation rates (and, thus, increase organ transplant activity) and developed recommen-

dations about organ donation to be used by European healthcare policy makers.

- Eulod [76] (EUropean Living Organ Donation, 2010–12, FP7): this project focused on living organ donation as a complementary approach to bridge the gap between demand for and supply of organs. Living organ donation presents opportunities, but it also involves ethical, legal and psychosocial implications. As a response to these challenges, this project was set up to increase collaboration between EU member states in order to improve the exchange of best practice on living organ donation programmes.
- Project EDD [77] (European Donation Day, 2009–11) aimed to develop guidelines for organising European organ donation days. The EDD celebration is envisaged as becoming the primary awareness-raising 'voice' for events promoting organ and tissue donation and transplantation in Europe. The main goal of this project was to propose tools and examples to help in the organisation of such events.
- Efretos [78] (European FRamework for the Evaluation of Organ TransplantS, 2009–11): the general objective of this project was to provide a common definition of terms and a methodology to evaluate the results of transplantation by promoting a compendium of follow-up registries. In the long term, a Europe-wide registry could enable the monitoring of patients and the evaluation of transplant results, and lead to a more efficient and safer organ allocation system.
- The Elpat Conferences [79] (Ethical, Legal and Psychosocial Aspects of Transplantation), organised by this section of the European Society for Organ Transplantation, were also supported by the European Commission in 2003, 2007 and 2010.
- Eulid [80] (EUropean LIving Donation and Public Health, 2008–10) and Elipsy [81] (European LIving Donor – PSYchosocial Follow-up, 2010–12) were projects led by the same consortium as the Lidobs Conference [82] (LIving Donor OBServatory, 2014): the main objective of these two projects and the conference was to make recommendations about adequate legal and ethical frameworks, living donor protection practices and long-term psychosocial and quality-of-life follow-up of living donors. It also aimed at creating tools and standardising protocols for the follow-up of living donors throughout Europe, to guarantee their health and safety.
- Etpod [83, 84] (European Training Program on Organ Donation, 2009): this project designed a professional European training programme on organ donation at different levels of involvement, in order to increase knowledge about organ donation, to maximise the rate of organ donation and to disseminate reliable information to the EU community.
- Transplant Co-ordinators 'Train the Trainers' course (2010–11): the European Commission encourages its member states to appoint and train donor co-ordinators in all hospitals where there is potential for organ donation. To help achieve this objective, the Commission contracted a consortium formed by Iavante and the Spanish ONT to train 80 donor co-ordinators from all of its member states, and to provide them with the necessary knowledge to replicate this training at national level.
- Odequs [85] (Organ Donation European QUality System, 2011–13) created useful evaluation tools to increase the efficiency of organ donation in all European countries. Differences between countries in national donation rates and in the effectiveness of donation programmes can be partly explained by the type of donation programmes implemented, but other issues – such as the structure of their donation services, their efficiency and social factors – have a big impact. The main objective of the project was to define a methodology to assess the performance of organ procurement at hospital level, including an audit system.
- Coorenor [86] (COORdinating a European initiative among National ORganisations for organ transplantation, 2010–12) established a co-ordinated network between existing national programmes in the field of organ transplantation, taking into account some major issues such as deceased donation, living donation and organ exchange.
- The joint action Mode [87] (Mutual Organ Donation and Transplantation Exchanges, 2010–11) aimed at improving and developing deceased organ donation and transplantation programmes. The project targeted the transfer of best practice and the creation of positive synergies among participating EU member states to support authorities in decision-making and policy contexts. The main issues tackled were donation/transplantation laws, transplant activities, brain death diagnosis and quality

programmes for donation/transplantation, traceability, structures and organisational networks.

- The joint action ACCORD [88] (Achieving Comprehensive Coordination in ORgan Donation throughout the European Union, 2012–15) aimed at improving co-operation between intensive care units and donor co-ordinators to facilitate deceased donation, proposing guidance and tools for the development of national and supranational living donor registries, and exchanging best practice through twinning activities.
- The joint action FOEDUS [89] (Facilitating Exchange of Organs Donated in EU Member States 2013–16) focused on facilitating collaboration on organ donation between national authorities in the EU. An IT tool was developed to enable quick organ offers or urgent requests between countries.
- EDITH [90] (2017–19) was a project co-financed by the European Commission that aimed to assess the different treatments for end-stage kidney disease currently used across the EU and to examine the factors that influence the different treatment choices. EDITH supported the establishment of follow-up registries in order to collect crucial information that could help to improve the quality and safety of living donors and all transplant recipients.
- EUDONORGAN [91] (2017–19) aimed at training and rising social awareness for increasing organ donation in the EU and neighbouring countries. Its activities were oriented to healthcare professionals and other relevant players such as: patients and patient support groups, public and governmental agencies, representatives of health institutions, opinion leaders and the media.

Some projects funded by the EU in the field of tissues and cells, addressing inspection standards or vigilance and safety, were also relevant to the field of organ transplantation, such as:

- EUSTITE [92] (EUropean Standards and Training in the Inspection of Tissue Establishments) and
- SoHO V&S [93] (Vigilance and Surveillance of Substances of Human Origin).

Finally, organ transplantation research has also been supported in successive EU framework programmes for research and innovation, including the projects BIO-DRIM (Biomarker-Driven personalised Immunosuppression) [94], COPE (Consortium on Organ Preservation in Europe) [95], HepaMAb (Human monoclonal antibody therapy to prevent hepatitis C virus reinfection of liver transplants) [96] and the ONE Study (A unified approach to evaluating cellular immunotherapy in solid-organ transplantation) [97]. All these projects have strengthened collaboration among national health authorities and between these latter and the professional associations in the area of organ donation and transplantation, allowing continuous input from the field into the regulatory framework and vice versa.

Additionally, to support initiatives outside the EU, some support is also provided in the field via Technical Assistance and Information EXchange (TAIEX) grants [98], managed by the Directorate-General of Enlargement of the European Commission and EU delegations in the different countries. TAIEX supports partner countries with regard to the interpretation, application and enforcement of EU legislation.

1.5.4. Other organisations and associations

Kidney transplant physicians and surgeons met in Amsterdam, the Netherlands, in April 2004 for the International Forum on the Care of the Live Kidney Donor. The objective of the Amsterdam Forum was to develop an international standard of care with a position statement from The Transplantation Society (TTS) on the responsibility of the community towards living kidney donors [99, 100]. A subsequent international conference of transplant physicians, surgeons and allied health professionals was held in Vancouver, Canada. The Vancouver Forum was convened under the auspices of TTS and its objective was to develop an international standard of care for live lung, liver, pancreas and intestinal organ donors [101].

The Declaration of Istanbul on Organ Trafficking and Transplant Tourism [19] was adopted in 2008 as an initiative of TTS and the International Society of Nephrology. It was updated in 2018 [102]. This declaration complements efforts by professional societies, national health authorities and intergovernmental organisations to support the development of ethical programmes for organ donation and transplantation, and to prevent organ trafficking and transplant tourism. The declaration defined financial neutrality in organ donation, non-resident, organ trafficking, resident, self-sufficiency in organ donation and transplantation, trafficking in persons for the purpose of organ removal, transplant tourism and travel for transplantation, and the declaration also provided principles of practice based on these definitions. Travel for transplantation is the move-

ment of persons across jurisdictional borders for transplantation purposes. Travel for transplantation becomes transplant tourism either (a) if it involves trafficking in persons for the purpose of organ removal or trafficking in human organs, or (b) if the resources (organs, professionals and transplant centres) devoted to providing transplants to non-resident patients undermine the country's ability to provide transplant services for its own population.

The European Society for Organ Transplantation (ESOT) was founded over 30 years ago and is dedicated to the pursuit of excellence in organ transplantation. The European Donation and Transplant Coordination Organisation (EDTCO) is a visible and active section within ESOT, intended to deal with all aspects of deceased and living donation, clinical co-ordination and procurement. EDTCO provides continuous training and education of donor co-ordinators and all other professionals with an interest in the area of donation and procurement. EDTCO promoted the development of the Certification of European Transplant Co-ordinators (CETC) project placed under the auspices of the European Union of Medical Specialists (UEMS) to ensure co-ordinators are offered the possibility of standardised recognition of their knowledge and expertise.

The Centre for Evidence in Transplantation (CET) was established by Sir Peter Morris in 2005. The Centre is devoted to evaluating the quality of evidence in solid organ transplantation and defines knowledge gaps in these different areas. The Centre produces systematic reviews based in general on randomised control trials, remembering that systematic reviews are Level 1 evidence in the medical field.

The World Medical Association (WMA), founded in 1947, has the central objective of establishing and promoting the highest possible standards of ethical behaviour and care by physicians. Within this framework, the WMA has produced a set of global policy statements in the field of organ and tissue donation and transplantation [103-105]. In 2020, in its 71st General Assembly, the WMA adopted a Statement on Measures for the Prevention and Fight against Transplant-Related Crimes, with recommendations of both a legislative and non-legislative nature, targeted to policy-makers, health authorities, physicians and other health professionals to prevent trafficking in persons for the purpose of organ removal and trafficking in human organs, to prosecute these crimes and to protect their victims [105].

1.6. References

1. Global Observatory on Donation and Transplantation [available at www.transplant-observatory.org, accessed 23 August 2021].
2. International figures on donation and transplantation 2019. *Newsletter Transplant* 2020;25(1) [available with archive at www.edqm.eu/en/organ-transplantation-reports-73.html, accessed 23 August 2021].
3. Joint Council of Europe/United Nations study on Trafficking in organs, tissues and cells and trafficking in human beings for the purpose of the removal of organs [available at www.edqm.eu/medias/fichiers/Joint_Council_of_EuropeUnited_Nations_Study_on_tra1.pdf; with Executive Summary, available at https://rm.coe.int/168070caab.
4. Council of Europe, Organs, tissues and cells technical guides [available at www.edqm.eu/en/organ-tissues-cells-transplantation-guides-1607.html, accessed 25 August 2021] and Council of Europe Blood Guide [available at www.edqm.eu/en/blood-transfusion-guides-1608.html, accessed 23 August 2021].
5. Conclusions of the 3rd Conference of European Health Ministers (1987), 16-17 November 1987 [available at https://rm.coe.int/CoERMPublicCommonSearchServices/DisplayDCTMContent?documentId=0900001680 4c6d07, accessed 23 August 2021].
6. European Directorate for the Quality of Medicines & HealthCare (EDQM) [available at www.edqm.eu, accessed 23 August 2021].
7. European Committee on Organ Transplantation (CD-P-TO) [available at www.edqm.eu/en/organ-transplantation-work-programme-72.html, accessed 23 August 2021].
8. Rahmel A. Vascularized composite allografts: procurement, allocation, and implementation. *Curr Transplant Rep* 2014;1(3):173-82.
9. Eurotransplant [available at www.eurotransplant.org/professionals/allocation, accessed 23 August 2021].
10. Oedingen C, Bartling T, Mühlbacher *et al.* Systematic review of public preferences for the allocation of donor organs for transplantation: principles of distributive justice. Springer Nature Switzerland AG *Patient* 2019 Oct;12(5):475-89.
11. O'Dell HW, McMichael BJ, Lee S *et al.* Public attitudes toward contemporary issues in liver allocation. *Am J Transplant* 2019 Apr;19(4):1212-17. https://doi.org/10.1111/ajt.15227.
12. Neuberger J, Ubel PA. Finding a place for public preferences in liver allocation decisions. *Transplantation* 2000 Nov 27;70(10):1411-13.
13. Recommendation Rec (2006) 15 of the Committee of Ministers to member states on the background, functions and responsibilities of a national transplant

organisation [available at www.edqm.eu/en/legal-framework, accessed 23 August 2021].

14. Council of Europe (1997), Convention for the Protection of Human Rights and Dignity of the Human Being with regard to the Application of Biology and Medicine: Convention on Human Rights and Biomedicine [the Oviedo Convention, available at http://conventions.coe.int/Treaty/en/Treaties/Html/164.htm, accessed 23 August 2021].
15. Council of Europe (2002), Additional Protocol to the Convention on human rights and biomedicine, on transplantation of organs and tissues of human origin [available at http://conventions.coe.int/Treaty/en/Treaties/Html/186.htm, accessed 23 August 2021].
16. Council of Europe Committee of Ministers, Resolution (78) 29 on harmonisation of legislations of member states relating to removal, grafting and transplantation of human substances [available at www.coe.int/t/dg3/healthbioethic/texts_and_documents/Res (78) 29E.pdf, accessed 23 August 2021].
17. World Health Organization (2010), WHO guiding principles on human cell, tissue and organ transplantation [available at www.who.int/transplantation/Guiding_PrinciplesTransplantation_WHA63.22en.pdf, accessed 23 August 2021].
18. Steering Committee of the Istanbul Summit (2008). Organ trafficking and transplant tourism and commercialism: the Declaration of Istanbul. *Lancet* 2008; 372(9632):5-6.
19. The Declaration of Istanbul Custodian Group (2008), The Declaration of Istanbul on Organ Trafficking and Transplant Tourism [available at www.declarationofistanbul.org/the-declaration, accessed 23 August 2021].
20. Council of Europe (2018), Guide for the implementation of the principle of prohibition of financial gain with respect to the human body and its parts from living or deceased donors [available at https://rm.coe.int/guide-financial-gain/16807bfc9a, accessed on 25 August 2021].
21. Report from the Nuffield Council on Bioethics Human bodies: donation for medicine and research [available at http://nuffieldbioethics.org/project/donation/, accessed 23 August 2021].
22. Council of Europe Committee of Ministers, Resolution CM/Res (2017) 1 on principles for the selection, evaluation, donation and follow-up of the non-resident living organ donors [available at www.edqm.eu/sites/default/files/cmres_2017_1-on_principles_for_selection_eval_donation_and_follow_up_of_nrld.pdf, accessed on 25 August 2021].
23. Council of Europe (2015), Convention against Trafficking in Human Organs, CETS No. 216 [available at https://rm.coe.int/16806dca3a, accessed 23 August 2021].
24. Council of Europe, *Conventions, Resolutions, Recommendations and Reports in the field of organs, tissues and cells* [available at www.edqm.eu/en/organ-transplantation-recommendations-resolutions-74.html, accessed 23 August 2021].
25. Convention for the Protection of Human Rights and Fundamental Freedoms [available at www.coe.int/en/web/conventions/full-list/-/conventions/treaty/005, accessed 23 August 2021].
26. European Agreement on the Exchange of Therapeutic Substances of Human Origin [available at http://conventions.coe.int/Treaty/en/treaties/html/026.htm, accessed 23 August 2021].
27. European Agreement on the Exchange of Tissue-Typing Reagents [available at http://conventions.coe.int/Treaty/en/treaties/html/084.htm, accessed 23 August 2021].
28. Additional Protocol to the European Agreement on the Exchange of Tissue-Typing Reagents [available at http://conventions.coe.int/Treaty/en/treaties/html/089.htm, accessed 23 August 2021].
29. Council of Europe Convention on Action against Trafficking in Human Beings and its Explanatory Report [available at http://conventions.coe.int/treaty/en/Treaties/Html/197.htm, accessed 23 August 2021].
30. Explanatory Report to the Council of Europe Convention against Trafficking in Human Organs [available at https://rm.coe.int/16800d3840].
31. EDQM (c. 1997), *Organ shortage: current status and strategies for the improvement of organ donation – a European consensus document* [available at www.edqm.eu/medias/fichiers/Organ_shortagecurrent_status_and_strategies_for_improvement_of_organ_donation_A_European_consensus_document.pdf, accessed 23 August 2021].
32. Council of Europe, *Resolutions, recommendations and reports related to safety, quality and ethical matters concerning procurement, storage and transplantation of organs, tissues and cells* [available at www.edqm.eu/en/reports-and-publications, accessed 27 August 2021].
33. Recommendation No. R (97) 15 of the Committee of Ministers to member states on xenotransplantation [available at www.coe.int/t/dg3/healthbioethic/texts_and_documents/Rec (97) 15E.pdf, accessed 23 August 2021].
34. Recommendation No. R (97) 16 of the Committee of Ministers to member states on liver transplantation from living related donors [available at www.edqm.eu/en/legal-framework, accessed 23 August 2021].
35. Recommendation Rec (2001) 5 of the Committee of Ministers to member states on the management

of organ transplant waiting lists and waiting times [available at www.edqm.eu/en/legal-framework, accessed 23 August 2021].

36. Recommendation Rec (2003) 10 of the Committee of Ministers to member states on xenotransplantation [available at www.edqm.eu/en/legal-framework, accessed 23 August 2021].
37. Explanatory memorandum to Recommendation Rec (2003) 10 [available at www.edqm.eu/medias/fichiers/Explanatory_memorandum_to_Recommendation_Rec200310.pdf, accessed 23 August 2021].
38. Recommendation Rec (2003) 12 of the Committee of Ministers to member states on organ donor registers [available at www.edqm.eu/sites/default/files/recommendation_no_2003_12_of_the_committee_of_ministers_to_member_states_on_organ_donor_registers.pdf, accessed 23 August 2021].
39. Recommendation Rec (2004) 7 of the Committee of Ministers to member states on organ trafficking [available at www.edqm.eu/sites/default/files/recommendation_no_2004_7_of_the_committee_of_ministers_to_member_states_on_organ_trafficking.pdf, accessed 23 August 2021].
40. Recommendation Rec (2004) 19 of the Committee of Ministers to member states on criteria for the authorisation of organ transplantation facilities [available at www.edqm.eu/sites/default/files/recommendation_no_2004_19_of_the_committee_of_ministers_to_member_states_on_criteria_for_the_authorisation_of_organ_transplantation_facilities.pdf, accessed 23 August 2021].
41. Recommendation Rec (2005) 11 of the Committee of Ministers to member states on the role and training of professionals responsible for organ donation (transplant 'donor co-ordinators') [available at www.edqm.eu/sites/default/files/recommendation_no_2005_11_of_the_committee_of_ministers_to_member_states_on_the_role_and_training_of_professionals_responsible_1.pdf, accessed 23 August 2021].
42. Recommendation Rec (2006) 16 of the Committee of Ministers to member states on quality improvement programmes for organ donation [available at www.edqm.eu/en/legal-framework, accessed 23 August 2021].
43. Council of Europe Committee of Ministers, Resolution CM/Res (2008) 4 on adult-to-adult living donor liver transplantation [available at www.edqm.eu/en/legal-framework, accessed 23 August 2021].
44. Council of Europe Committee of Ministers, Resolution CM/Res (2008) 6 on transplantation of kidneys from living donors who are not genetically related to the recipient [available at www.edqm.eu/en/legal-framework, accessed 23 August 2021].
45. Council of Europe Committee of Ministers, Resolution CM/Res (2013) 55 on establishing procedures for the collection and dissemination of data on transplantation activities outside a domestic transplantation system [available at www.edqm.eu/sites/default/files/medias/fichiers/resolution_cmres201355_on_establishing_procedures_for_the_collection_and_dissemination_of_data_on_tr.pdf, accessed 23 August 2021].
46. Council of Europe Committee of Ministers, Resolution CM/Res (2013) 56 on the development and optimisation of live kidney donation programmes [available at www.edqm.eu/sites/default/files/medias/fichiers/resolution_cmres201356_on_the_development_and_optimisation_of_live_kidney_donation_programmes.pdf, accessed 23 August 2021].
47. Council of Europe Committee of Ministers, Explanatory Memorandum to Resolution CM/Res (2013) 56 [available at www.edqm.eu/sites/default/files/explanatory_memorandum_cm_2013145.pdf, accessed 23 August 2021].
48. Council of Europe Committee of Ministers, Resolution CM/Res (2015) 10 on the role and training of critical care professionals in deceased donation [available at www.edqm.eu/sites/default/files/resolution_cmrs_201510_role_and_training_critical_care_professionals_in_deceased_donation.pdf, accessed 23 August 2021].
49. Council of Europe Committee of Ministers, Resolution CM/Res (2015) 11 on establishing harmonised national living donor registries with a view to facilitating international data sharing [available at www.edqm.eu/sites/default/files/resolution_on_establishing_harmonised_national_living_donor_registries_with_a_view_to_facilitating_international_data_sharing_2015_11.pdf, accessed 23 August 2021].
50. Council of Europe Committee of Ministers, Explanatory Memorandum to Resolution CM/Res (2015) 11 [available at www.edqm.eu/sites/default/files/explanatory_memorandum_resolution_cm_res201511_on_harmonised_national_living_donor_registries_2015.pdf, accessed 23 August 2021].
51. Council of Europe Committee of Ministers, Resolution CM/Res (2017) 2 on establishing procedures for the management of patients having received an organ transplant abroad upon return to their home country to receive follow-up care [available at www.edqm.eu/sites/default/files/cmres_2017_2-on_establishing_procedures_for_patients_received_organ_tx_abroad.pdf, accessed 23 August 2021].
52. Recommendation CM/Rec (2020) 4 of the Committee of Ministers to member States on the quality and safety of organs for transplantation [available at https://search.coe.int/cm/Pages/result_details.aspx?Object

Id=0900001680 9fdcdd#_ftn1, accessed on 26 August 2021].

53. Recommendation CM/Rec (2020) 5 of the Committee of Ministers to member States on the quality and safety of tissues and cells for human application [available at https://search.coe.int/cm/Pages/result_details.aspx?ObjectId=0900001680 9fdcde, accessed on 26 August 2021].
54. Recommendation CM/Rec (2020) 6 of the Committee of Ministers to member States on establishing harmonised measures for the protection of haematopoietic progenitor cell donors [available at https://rm.coe.int/0900001680 9fdd5b, accessed on 26 August 2021].
55. World Health Assembly (1991), Human organ transplantation: WHA44.25 [available at www.transplant-observatory.org/download/resolution-wha44-25-endorsing-the-1991-guiding-principles/, accessed 26 August 2021].
56. World Health Assembly (2010), Human organ and tissue transplantation: WHA63.22 [available at http://apps.who.int/gb/ebwha/pdf_files/WHA63/A63_R22-en.pdf, accessed 23 August 2021].
57. World Health Assembly (2004), Human organ and tissue transplantation: WHA57.18 [available at http://apps.who.int/gb/ebwha/pdf_files/WHA57/A57_R18-en.pdf, accessed 23 August 2021].
58. Centro Nazionale Trapianti (2011), *Notify: Exploring vigilance notification for organs, tissues and cells*, Editrice Compositori, Bologna [available at www.transplant-observatory.org/SiteCollectionDocuments/glorepnotify.pdf, accessed 23 August 2021].
59. World Health Organization. Aide-mémoire on access to safe and effective cells and tissues for transplantation [available at https://apps.who.int/iris/handle/10665/342055, accessed 23 August 2021].
60. World Health Organization. Aide-mémoire on key safety requirements for essential minimally processed human cells and tissues for transplantation [available at www.who.int/transplantation/AM_HCTTmin_requirements.pdf, accessed 23 August 2021].
61. United Nations General Assembly resolution 73/189 on Strengthening and promoting effective measures and international cooperation on organ donation and transplantation to prevent and combat trafficking in persons for the purpose of organ removal and trafficking in human organs [available at https://digitallibrary.un.org/record/1661225?ln=en, accessed 26 August 2021].
62. European Union: European Commission General Directorate on Public Health, Organ Transplantation Section [available at https://ec.europa.eu/health/blood_tissues_organs/overview_en, accessed 23 August 2021].
63. Treaty on the Functioning of the European Union [available at https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=celex%3A12012E%2FTXT, accessed 25 August 2021].
64. European Parliament and Council of the European Union: Directive 2010/53/EU of the European Parliament and of the Council of 7 July 2010 on standards of quality and safety of human organs intended for transplantation. Official Journal of the European Union 2010;(53):14-29 [available at https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=LEGISSUM%3Aspo0008, accessed 25 August 2021].
65. Corrigendum to Directive 2010/45/EU [available at https://eur-lex.europa.eu/legal-content/EN/ALL/?uri=CELEX%3A32010L0053R%2801%29, accessed 25 August 2021].
66. Commission Implementing Directive 2012/25/EU of 9 October 2012 laying down information procedures for the exchange, between member states, of human organs intended for transplantation [available at https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=celex%3A32012L0025, accessed 25 August 2021].
67. European Commission Campaign 'Europe for Patients' on organ donation and transplantation: Commission Action plan on Organ Donation and Transplantation (2009-2015) [information available at https://healthcare-in-europe.com/en/news/a-new-tool-for-european-patients.html, accessed 23 August 2021].
68. European Commission (2008), Communication from the Commission: Action Plan on Organ Donation and Transplantation (2009-2015): Strengthened Cooperation between Member States [available at https://ec.europa.eu/health/ph_threats/human_substance/oc_organs/docs/organs_action_en.pdf, accessed 23 August 2021].
69. Council of the EU (2012), Council conclusions on organ donation and transplantation (2012/C 396/03) of EU member states [available at https://ec.europa.eu/health/sites/health/files/blood_tissues_organs/docs/organs_council_ccl_2012_en.pdf, accessed 25 August 2021].
70. Actor study: Study on the set-up of organ donation and transplantation in the EU member states, uptake and impact of the EU Action Plan on Organ Donation and Transplantation (2009–2015) [available at http://ec.europa.eu/health/blood_tissues_organs/docs/organs_actor_study_2013_en.pdf, accessed 25 August 2021].
71. European Commission (2014), Commission Staff Working Document on the mid-term review of the EU Action Plan on Organ Donation and Transplantation [available at http://ec.europa.eu/health/blood_

tissues_organs/docs/midtermreview_actionplan_organ_en.pdf, accessed 25 August 2021].

72. Factor study. A study on the uptake and impact of the EU action plan on organ donation and transplantation (2009–2015) in the EU member states. [available at www.nivel.nl/nl/publicatie/study-uptake-and-impact-eu-action-plan-organ-donation-and-transplantation-2009-2015-eu, accessed on 26 August 2021].
73. EU Programmes of Community Action in the Field of Health [more information available at https://ec.europa.eu/health/sites/health/files/programme/docs/second_healthprogramme_implementation_2012_en.pdf and in Ex-post evaluation of the 2nd Health Programme 2008-2013, available at https://ec.europa.eu/health/programme/policy/2008-2013/evaluation_en, accessed 25 August 2021].
74. Alliance-O (European Group for Co-ordination of National Research Programmes on Organ Donation and Transplantation) [available at www.era-learn.eu/network-information/networks/alliance-o, accessed 25 August 2021].
75. Dopki (Improving Knowledge and Practices in Organ Donation) [available at www.ont.es/internacional/Documents/Dopki.pdf, accessed 25 August 2021].
76. Eulod (European Living Organ Donation) [available at www.ceu.edu/project/eulod-european-living-organ-donation, accessed 25 August 2021].
77. Project EDD [available at www.europeandonationday.eu/, accessed 27 August 2021].
78. Efretos (European Framework for the Evaluation of Organ Transplants) [available at http://beta.eurotransplant.org/cms/index.php?page=efretos, accessed 25 August 2021].
79. Elpat Conferences on the ethical, legal and psychosocial aspects of transplantation [available at https://esot.org/elpat/, accessed 25 August 2021].
80. Eulid (European Living Donation and Public Health) [available at www.eulivingdonor.eu/eulid/what-is-eulid.html, accessed 25 August 2021].
81. Elipsy (European Living Donor – Psychosocial Follow-up) [available at www.eulivingdonor.eu/elipsy, accessed 25 August 2021].
82. Lidobs Conference (Living Donor Observatory) [available at www.eulivingdonor.eu/lidobs, accessed 25 August 2021].
83. Etpod (European Training Program on Organ Donation) [available at www.etpod.eu, accessed 25 August 2021].
84. Manyalich M, Guasch X, Paez G *et al.* Etpod (European Training Program on Organ Donation): a successful training program to improve organ donation. *Transpl Int* 2013;26(4):373-84.
85. Project Odequs (Organ Donation European Quality System) [available at www.odequs.eu, accessed 25 August 2021].
86. Coorenor (Coordinating a European initiative among national organisations for organ transplantation) [information available at www.agence-biomedecine.fr/European-programmes?lang=fr, accessed 25 August 2021].
87. Joint action Mode (Mutual Organ Donation and Transplantation Exchanges) [information available at https://archpublichealth.biomedcentral.com/articles/10.1186/0778-7367-71-3, accessed 25 August 2021].
88. Joint action Accord (Achieving Comprehensive Coordination in Organ Donation throughout the European Union) [available at www.accord-ja.eu, accessed 25 August 2021].
89. Joint Action Foedus (Facilitating Exchange of Organs Donated in EU Member States) [available at www.foedus-eoeo.eu/#/public, accessed 25 August 2021].
90. Eudorgan project [available at http://eudonorgan.eu/, accessed 23 August 2021].
91. Edith project [available at http://edith-project.eu/, accessed 23 August 2021].
92. Eustite project (European Standards and Training in the Inspection of Tissue Establishments) [available at www.notifylibrary.org/content/european-union-standards-and-training-inspection-tissue-establishments-project-eustite, accessed 28 August 2021].
93. SoHO V&S project (Vigilance and Surveillance of Substances of Human Origin) [available at www.notifylibrary.org/content/vigilance-and-surveillance-substances-human-origin-project-sohovs, accessed 25 August 2021].
94. Bio-Drim project (BIOmarker-Driven personalised immuno-suppression) [available at www.biodrim.eu, accessed 25 August 2021].
95. Cope project (Consortium on organ preservation in Europe) [available at www.cope-eu.org, accessed 25 August 2021].
96. HepaMAb project (Human monoclonal antibody therapy to prevent hepatitis C virus reinfection of liver transplants) [information available at https://cordis.europa.eu/project/id/305600/reporting, accessed 25 August 2021].
97. One Study (A unified approach to evaluating cellular immunotherapy in solid-organ transplantation) [available at www.onestudy.org, accessed 25 August 2021].
98. Technical Assistance and Information Exchange (TAIEX) [available at http://ec.europa.eu/enlargement/tenders/taiex/index_en.htm, accessed 25 August 2021].
99. Ethics Committee of The Transplantation Society. Consensus statement of the Amsterdam Forum on

the care of the live kidney donor. *Transplantation* 2004;78(4):491-2 [available at www.tts.org/images/stories/pdfs/ConsensusStatementfinal.pdf, accessed 25 August 2021].

100. Ethics Committee of The Transplantation Society. A report of the Amsterdam Forum on the care of the kidney donor: data and medical guidelines – Amsterdam 2004 International Forum on the Care of the Live Kidney Donor. *Transplantation* 2005 Mar 27;79(6 Suppl): S53-S66 [available at www.who.int/transplantation/publications/ConsensusStatementShort.pdf, accessed 25 August 2021].
101. Barr ML, Belghiti J, Villamil FG *et al.* Report on the Vancouver Forum. *Transplantation* 2006;81(10): 1373-85 [available at www.tts.org/images/stories/pdfs/Vancouver_Forum.pdf, accessed 25 August 2021].
102. The Declaration of Istanbul on Organ Trafficking and Transplant Tourism (2018 Edition) [available at www.declarationofistanbul.org/images/Policy_Documents/2018_Ed_Do/2018_Edition_of_the_Declaration_of_Istanbul_Final.pdf, accessed 26 August 2021].
103. WHA Statement on Organ and Tissue Donation [available at https://www.wma.net/policies-post/wma-statement-on-organ-and-tissue-donation/, accessed 7 December 2021]
104. WMA Declaration of Sidney on the determination of death and the recovery of organs [available at https://www.wma.net/policies-post/wma-declaration-of-sydney-on-the-determination-of-death-and-the-recovery-of-organs/, accessed 7 December 2021]
105. WMA Statement on measures for the prevention and fight against transplant-related crimes [available at https://www.wma.net/policies-post/wma-statement-on-measures-for-the-prevention-and-fight-against-transplant-related-crimes/ accessed 7 December 2021].

Chapter 2. Identification and referral of possible deceased organ donors

2.1. Introduction

Through the Madrid Resolution, participants at the 3rd World Health Organization (WHO) Global Consultation on Organ Donation and Transplantation, held in Madrid (Spain) in 2010, called on governments and healthcare professionals to pursue self-sufficiency in transplantation, that is, to comprehensively satisfy the transplantation needs of their patients by using resources from within their own population [1]. Self-sufficiency entails a combination of strategies targeted at decreasing the burden of diseases treatable through transplantation and at maximising the availability of organs for transplantation, with priority given to donation from deceased donors. Deceased organ donation is an essential component of self-sufficiency. Countries that have achieved the highest transplantation rates – and best access of their patients to transplant therapy – are those with well-established deceased donation programmes [2].

Donation after the determination of death by neurological criteria, also known as donation after brain death (DBD), represents the main source of solid organs from deceased donors. However, the persisting shortfall in the availability of organs and the technical advances in the field have prompted many countries to introduce programmes of donation after the circulatory determination of death (DCD). DCD donors already represent 21 % of all deceased organ donors reported to the Global Observatory on Donation and Transplantation (2017 data), even though this activity is developed only in a limited number of countries because of legal, organisational and technical constraints specific to this type of donation [3].

Donation from deceased donors is a complex process, a sequence of procedural steps which must be properly realised to achieve successful organ transplantation. The Madrid Resolution resulted in a list of practical recommendations for self-sufficiency in transplantation and the publication of the WHO Critical Pathway for Deceased Donation, classifying organ donors on the basis of the phases of the deceased donation process [4]. The Madrid Resolution also stated that, in pursuing self-sufficiency in transplantation, donation should be included as a consideration in every end-of-life care pathway. This recommendation is consistent with the generally accepted principle that the treating physician or team should respect the overall best interests of the dying patient in the decision-making process at the end of life [5]. This assessment of best interests is not based simply on the patient's medical or clinical interests, but should include a more holistic approach, where the patient's values, beliefs and preferences are also taken into account, including their wishes to donate (or not donate) their organs after death [6][7][8].

Although some aspects of deceased donation are similar in both DBD and DCD, there are also important differences between the two, and DCD poses some very specific challenges. The identification and subsequent referral of organ donors by treating physicians, usually from intensive care units (ICUs) and emergency departments, to the donor co-ordinator

or staff of the corresponding organ procurement organisation (OPO) is the first and most crucial step of the deceased donation process. Organ donation cannot take place unless possible donors are identified and referred in a timely fashion, marking the beginning of either the DBD or the DCD organ donation pathway. Failure to identify and refer organ donors is in fact one of the main reasons for substantial differences in deceased donation rates between countries, regions and hospitals [9].

This chapter describes and structures the process of donation after death, both DBD and DCD, from the perspective of the WHO Critical Pathway for Deceased Donation [4]. It addresses the integration of organ donation into end-of-life care, and it then focuses on the steps of donor identification and referral. Recommendations on how to succeed in subsequent phases of the deceased donation process are provided in other chapters of this guide.

2.2. Types of deceased donor based on the criteria used to determine death

There are two deceased organ donation pathways, depending on the criteria used to determine death before the procurement of organs: DBD and DCD. DBD refers to donation from persons who have been declared dead based on the irreversible loss of neurological functions. Confirmation of death must comply with national legal requirements. Legislation related to the determination of death by neurological criteria varies from country to country, and determination of death must be undertaken in strict compliance with national protocols and guidelines.

DCD refers to donation from persons who have been declared dead using circulatory criteria. Depending on the clinical scenario in which cardiac arrest occurs, there are four different categories of DCD donors, first described in Maastricht (Netherlands) in 1995 and updated in Paris (France) in 2013 (see Table 2.1) [10][11]. Categories I and II describe donors whose death has occurred following an unexpected cardio-respiratory arrest – uncontrolled DCD (uDCD) donors – while category III describes donation from persons whose death has followed the planned withdrawal of life-sustaining therapy (WLST) – controlled DCD (cDCD) donors. Category IV may be controlled or uncontrolled, depending on whether the circulatory arrest in a person with a suspected or confirmed brain death (BD) condition was unexpected or planned.

Donation after circulatory death (DCD) is practised in a reduced number of countries across the world [12]. Some countries perform donation only from selected categories of such donors. The determination of death based on circulatory criteria also varies across countries, e.g. with regard to the period of observation required following the cardio-respiratory arrest. Detailed information on DCD practices is provided in Chapter 12.

2.3. The process of deceased donation: the WHO Critical Pathway

The WHO Critical Pathway for Deceased Donation [4] was conceived as a useful clinical tool applicable in every country (region or hospital) for assessing the potential of deceased organ donation, evaluating performance in the deceased donation process and identifying areas for improvement.

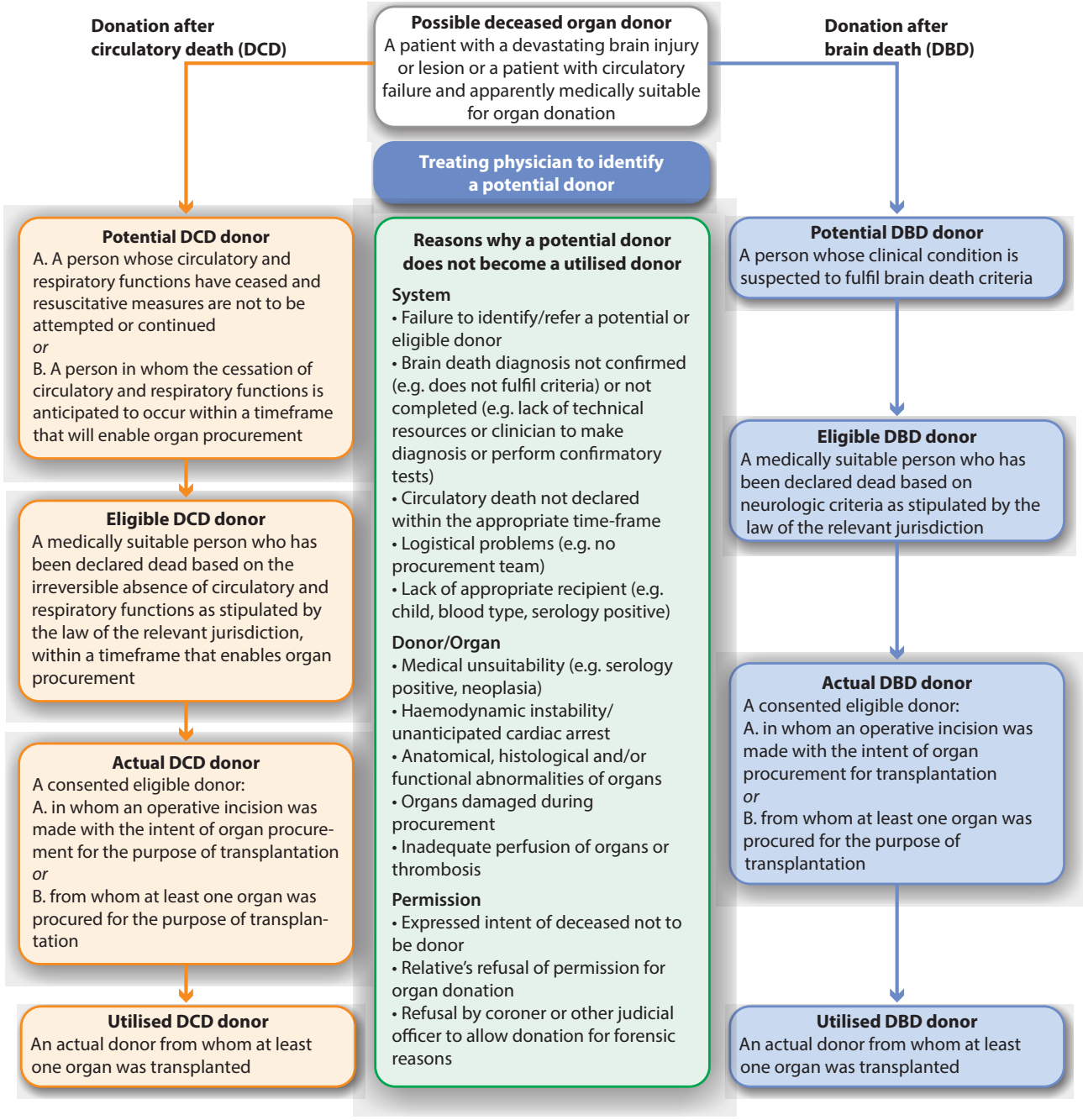
Table 2.1. **Donation after circulatory death: categories of donor**

Maastricht category and type of donation after circulatory death (DCD)	**Observations**
I: Found dead (uncontrolled)	Sudden unexpected cardiac arrest, with no attempt at resuscitation by a medical team
I.a: out of hospital	
I.b: in hospital	
II: Witnessed cardiac arrest (uncontrolled)	Sudden unexpected irreversible cardiac arrest, with unsuccessful resuscitation by a medical team
II.a: out of hospital	
II.b: in hospital	
III: Withdrawal of life-sustaining therapy (controlled DCD)*	Planned, expected cardiac arrest, following the withdrawal of life-sustaining therapy
IV: Cardiac arrest while brain dead (uncontrolled or controlled)	Sudden or planned cardiac arrest after diagnosis of brain death, but before organ procurement

Modified Maastricht classification, Paris 2013 [11].

* This category III mainly refers to the decision to withdraw life-sustaining therapies. Legislation in some countries allows euthanasia (medically-assisted cardiac arrest), and subsequent organ donation is described as an additional category.

Figure 2.1. **World Health Organization Critical Pathway for Deceased Donation**



The 'dead donor rule' must be respected. That is, patients may become donors only after death, and the procurement of organs must not cause a donor's death.

Adapted with permission from *Transpl Int* 2011;24(4):373-8 [4].

The particular value of this tool is that it creates uniformity in the description and assessment of the deceased donation process. The Critical Pathway for Deceased Donation addresses both DBD and DCD and defines types of donors based on the different phases of the donation process: possible, potential, eligible, actual and utilised organ donors (see Figure 2.1).

2.3.1. Possible deceased organ donor

A possible deceased organ donor is a patient, either with a devastating brain injury (DBI) or with a circulatory failure, who is apparently medically suitable for organ donation. The patient with a DBI is a patient with an imminent risk of death from a neurological insult and where the multidisciplinary team is considering not initiating or not continuing life-sustaining therapies on the grounds of futility in favour of palliative and end-of-life care. This is frequently a patient already admitted to an ICU and

receiving mechanical ventilation, but it can also be a patient outside the ICU in whom the decision has been made not to initiate or continue mechanical ventilation and/or not to admit to the ICU with a therapeutic purpose. Organ donation is possible in this particular scenario if intensive care is initiated or continued despite futility, that is, if intensive care to facilitate organ donation (ICOD) is applied as described in section 2.4.

A patient with circulatory failure is also a possible organ donor. If advanced cardio-pulmonary resuscitation (CPR) in a patient with a sudden cardiac arrest is considered to be unsuccessful, this would represent the starting point of the uDCD process.

The possible deceased organ donor with a DBI, as defined above, represents a common starting point of the two different pathways for deceased organ donation, DBD and/or cDCD, pathways that will be activated depending upon the outcome of the patient's condition, the end-of-life care practices and national legal frameworks.

The WHO Critical Pathway for Deceased Donation identifies the possible organ donor as the ideal starting point for identification and referral of donors by the treating physician or team to the donor co-ordinator or staff of the corresponding OPO in order to avoid late referrals. Early referral allows an appropriate assessment of medical suitability, careful preparation of the family approach and timely organisation of other logistical aspects of the deceased donation process. However, early referral is not considered appropriate or is not legally possible in all jurisdictions, which leads to the need for delay in referral, particularly in DBD, to the point where the person already exhibits clinical signs consistent with BD (brain death) or to the point where BD has already been declared as per national standards [1].

The emergency department is an important unit where possible organ donors can be identified and are, however, frequently missed. It is estimated that up to 50 % of actual DBD donors and up to 9 % of actual DCD donors are admitted from emergency departments. Failed identification of possible donors in the emergency department may be due to lack of knowledge of referral pathways or incorrect assumptions regarding eligibility criteria. This is why it is of utmost importance to educate personnel from the emergency department in referral criteria regarding DBD and/or DCD, where applicable.

2.3.2. Potential deceased organ donors

A potential DBD donor is a person whose clinical condition is consistent with BD.

A potential DCD donor is either:

- a person whose circulatory and respiratory functions have ceased and in whom CPR was attempted but was (or is now) considered unsuccessful and not to be continued (potential uDCD donor), or
- a person in whom CPR will not be attempted and the cessation of circulatory and respiratory functions is expected to occur within a timeframe that will enable organ procurement (potential cDCD donor).

This last scenario refers to persons with a DBI in whom further treatment has been deemed futile and for whom a decision has been made to withdraw life-saving treatment [11]. Potential cDCD donors also include patients with end-stage neurodegenerative or cardiac/respiratory diseases for whom a decision of WLST has been made because sustaining life is no longer in the best interests of the patient. Although the majority of actual cDCD donors die from DBI, data from the Netherlands, Spain and the United Kingdom suggest that up to 15 % of cDCD donors die from other non-neurological conditions.

The transition from possible to potential deceased organ donor depends on a variety of factors, particularly the end-of-life care practices in place. The Ethicus study, undertaken by the European Society of Intensive Care Medicine at the beginning of the 21st century, described the circumstances of death of patients dying in European ICUs. The study revealed that the incidence of BD was significantly higher in southern Europe compared to northern European countries (12.4 *v.* 3.2 %). On the other hand, the percentage of patients who died following WLST was significantly higher in northern Europe, compared with the south (47.4 *v.* 17.9 %). These findings highlight how WLST when further treatment is considered futile is frequent in northern Europe, but relatively rare in southern Europe. These different approaches to end-of-life care – in the particular context of a patient's death as a result of a DBI (possible organ donors) – were also evident in the Accord Joint Action project [13]. The Ethicus study has since been repeated, revealing that variations in end-of-life care patterns persist across European regions. However, compared with data reported from the same ICUs 15 years ago, limitations of life-sustaining therapies (withholding or WLST) are occurring significantly more frequently and death without limitations of life-prolonging therapies are occurring significantly less frequently. These data reveal that the potential for cDCD is becoming more frequent over time [14].

2.3.3. Eligible deceased organ donors

The eligible DBD donor is a medically suitable patient who has been declared dead based on neurological criteria as stipulated by the law of the relevant jurisdiction. An eligible DCD donor is defined as a patient who is medically suitable for organ donation and in whom death has been declared on the basis of circulatory criteria according to national standards. Death should also have occurred within a timeframe that enables organ procurement (see Chapter 12).

A potential DBD donor might not become eligible for organ donation because the diagnosis of death by neurological criteria has not been confirmed – e.g. because of a lack of the technical and human resources needed for confirmation. It is worth noting that in some European countries and the USA up to 30 % of patients who exhibit a clinical condition consistent with BD are not tested to confirm the diagnosis, a practice that completely removes the possibility of DBD [15]. In circumstances where BD is not confirmed, cDCD might be activated, but opting for cDCD in place of DBD should be avoided whenever possible, since the effectiveness of the DCD process is lower than that of DBD, and results of transplantation worse.

A potential cDCD donor might not be eligible for organ donation because death by circulatory criteria has not been determined within a time frame that allows organ procurement. cDCD will occur only if the cardio-respiratory arrest follows soon after WLST. This time limit has been most commonly established at 2 hours, but it is being extended in some countries (for example, to 3-4 hours in the United Kingdom), although death following WLST not infrequently occurs beyond this time limit [16].

In the uDCD setting, non-eligibility is frequently determined because of an excessive time to develop the process, which renders organs unsuitable for transplantation due to the deleterious effects of warm ischaemia on organ viability.

Potential donors (DBD or DCD) might also be ineligible because they are considered medically unsuitable. Although there are very few absolute contraindications to organ donation, a perception of medical unsuitability is a frequent reason for not referring potential donors to the donor co-ordinator or staff of the OPO. Moreover, external audits in some countries have revealed that 11 % of the decisions not to refer a potential DBD donor on medical grounds were incorrect [17]. A patient's suitability to donate organs is dependent on recipient factors as well as donor factors, and some organs may be acceptable for certain patients, whereas others may not. The primary role of the treating team is to identify and refer potential donors, but decisions regarding medical suitability for donation should be always left to the donor co-ordinator and the relevant transplant teams.

2.3.4. Actual deceased organ donors

An actual DBD and an actual DCD donor are defined in the same manner – as a consenting, eligible organ donor in whom an operative incision has been made with the intention of organ procurement for the purpose of transplantation. An actual deceased organ donor is also defined as a person from whom at least one organ has been retrieved for transplantation purposes.

The main reason why organ procurement does not proceed in an eligible organ donor is that consent/authorisation was declined, either by the individual during their lifetime or by their relatives. Consent rates to organ donation are influenced by a variety of factors – both modifiable and non-modifiable. In the Accord Joint Action [13], in a dedicated study undertaken at 67 hospitals from 15 EU member states, 24 % and 33 % of families approached to discuss organ donation declined authorisation for organ procurement, in the DBD and DCD processes respectively. The rate of declined consent for organ procurement in the DBD process was, however, underestimated since the rate referred only to those families approached to discuss organ donation from persons whose death was already confirmed by neurological criteria. The moment when the family is first approached to discuss organ donation has indeed an impact on consent rates [18]. In a Spanish study, consent was more frequent if the family was approached once the patient already fulfilled BD criteria or if the BD diagnosis had been completed, compared with situations when BD was likely but had not occurred yet [19]. These data reveal the more complex communication with the family in the context of ICOD.

2.3.5. Utilised deceased organ donors

Utilised DBD and DCD donors are defined as those actual DBD or DCD donors from whom at least one solid organ has been transplanted.

Once retrieved, organs might not be transplanted because of anatomical or histological findings in the donor or in the organs themselves, poor perfusion, organ damage during procurement or lack of suitable recipients, among others. Non-utilisation of actual donors is more frequent in the case of expanded-criteria donors (see Chapter 7) and in DCD in comparison to the DBD process (see Chapter 12).

Non-utilisation rates are also higher in uDCD than in the cDCD setting [3][12].

2.4. Intensive care to enable organ donation (ICOD)

A possible organ donor may be a person with a DBI in whom further therapy is deemed futile, either in the emergency department or in the hospital ward, and for whom admission to an ICU, and even the initiation of mechanical ventilation, is not deemed therapeutically indicated because neither procedure is considered to be in the patient's best clinical interest. In this context, intubation and initiation of mechanical ventilation – that is, elective non-therapeutic ventilation (ENTV) – and admission to an ICU could be considered with the purpose of incorporating the option of organ donation into the end-of-life care of the patient [20].

The potential for organ donation could be therefore considered in patients with a DBI, that is, patients with acute, severe neurological damage and an apparently hopeless prognosis, where the multidisciplinary team is considering a shift from active treatment to palliative and end-of-life care. In this situation, a patient with DBI and impending death could be considered for ICOD, which may include ENTV and continued organ support. In practice, this means admission to the ICU [21]. Candidates for ICOD are mainly identified in the emergency department, but also in hospital wards (neurology, neurosurgery and others). Close collaboration between OPO staff or donor co-ordinators, ICU personnel and professionals from the above-mentioned departments is necessary and thus represents a crucial starting point for the successful realisation of this particular donation practice.

Today, ICOD, inclusive of ENTV or not, is a common clinical practice in many but not all countries [14] since it still raises some ethical, legal, community and professional concerns in some settings [22][23]. What is clear is that ICOD and ENTV result in an increase in the total number of organs available for transplantation at a time when the pool of 'standard' DBD donors is decreasing because of reduced incidence of death from brain trauma and stroke [24][25][26-28][29]. ICOD also offers more patients the opportunity to donate organs after death if this is consistent with their wishes and values.

Since ICOD and ENTV are relatively new as successful organ-donation practices, a few details are discussed below.

In patients with a severe neurological injury, a consensus concerning the patient's prognosis and non-treatable condition should be established by an expert multidisciplinary team before ICOD is considered. The decision not to pursue active treatment should be based on scientific evidence, expert opinion, clinical experience and the patient's age and co-morbidity; moreover, it should be made on an individual, case-by-case basis [30].

Patients identified as potential candidates for ICOD and ENTV should be immediately referred to the donor co-ordinator or the staff of the corresponding OPO. Early referral allows enough time for the assessment of suitability for donation, reduces the delay for ICU admission and enables a planned approach to the patient's family. Clinical and radiological triggers facilitate the identification of possible donors and should be developed and recommended by a multidisciplinary expert team for adoption in every hospital with a potential for organ donation. Once referred, patients with a DBI should not be considered candidates for ICOD unless it is likely that BD will occur within a short period of time and the patient has no apparent medical contraindications to organ donation.

Although informed consent for ICOD and ENTV cannot be obtained from a patient with a DBI, these procedures can be considered to be in the patient's best interests if they are consistent with the patient's known moral values and beliefs, including any expressed wish to donate organs after death. Family consent must be obtained before using interventions that are intended to incorporate organ donation into end-of-life care. The patient's relatives must be given clear and understandable information that the prognosis is hopeless either for survival or an acceptable functional outcome, and that ICOD and ENTV are only to be introduced once they have accepted the decision that active treatment will not be pursued. The family should be informed that interventions will be initiated or continued to allow organ donation when the patient deteriorates to BD and that measures will be undertaken to avoid any potential distress, pain and discomfort. The family should be able to revoke their decision at any time.

Because the family is likely to experience initial shock and inability to make decisions, information should be provided in a gradual and progressive manner adapted to the emotional and other needs of the family. These complex communications with a patient's relatives need to be conducted by highly skilled staff with knowledge and experience in organ donation and in this particular type of interview (see Chapter 4). A large number of patients with DBI will have been intubated in a prehospital setting, facilitating a decision for ICOD while waiting until the

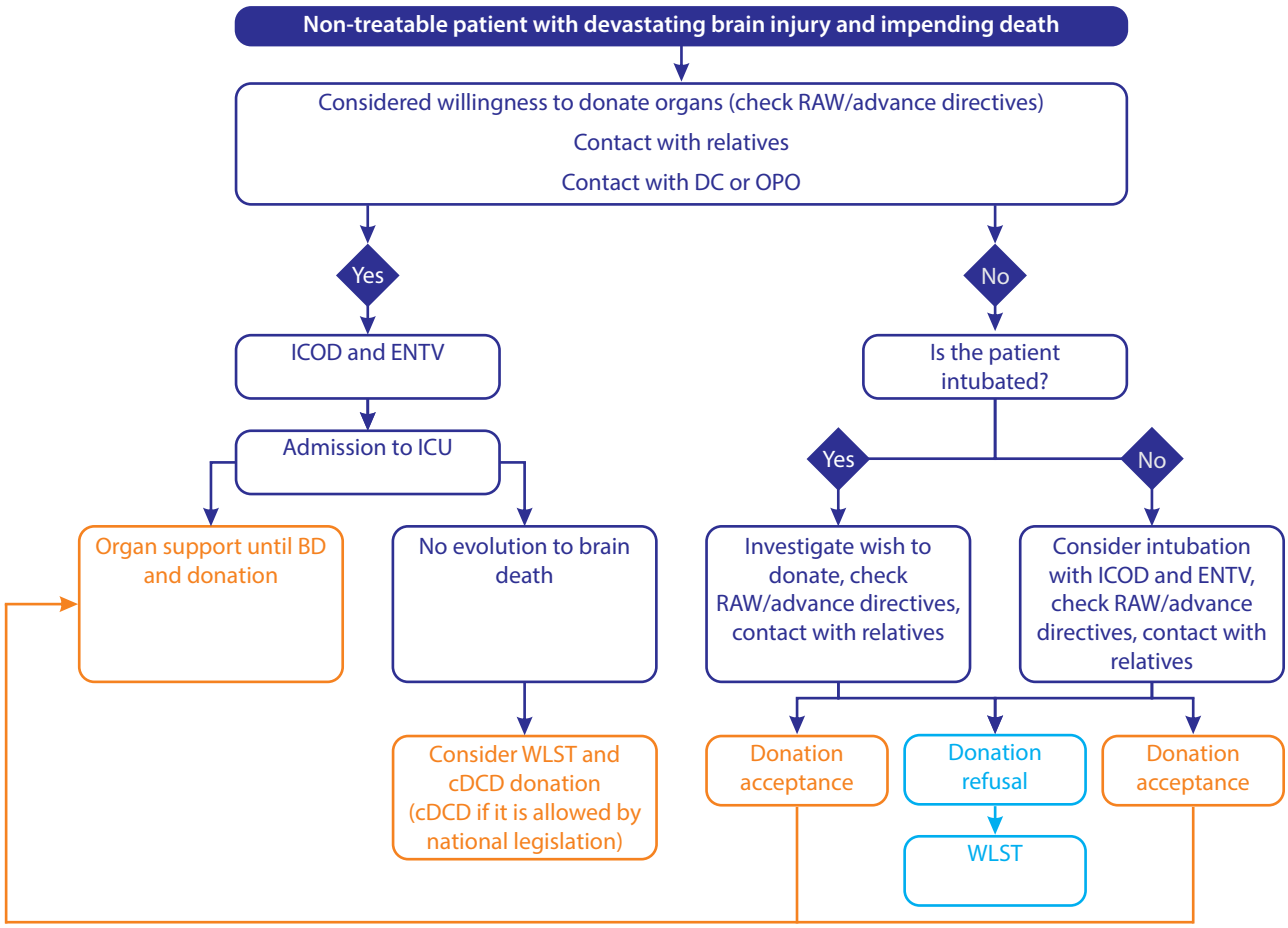
patient's and their family's wishes regarding organ donation have been established.

ICOD is not applicable only to patients with a DBI who are outside the ICU but also to dying patients with a hopeless neurological prognosis in the ICU who are not yet brain dead, and in whom the multidisciplinary ICU team has concluded that further invasive therapy no longer has a beneficial therapeutic effect. Although cDCD may be considered in this setting if it is allowed by national legislation, where BD is likely to occur within a short period of time, delaying WLST may be a preferred option to allow the confirmation of death using neurological criteria.

Once consent for ICOD – and ENTV – has been obtained, patients will be subject to mechanical ventilation and somatic organ-protective measures until BD is established and then until the procurement of transplantable organs. Sedation with or without analgesia should be provided to ensure the patient's comfort with drugs and doses that do not interfere with the subsequent BD diagnosis. The majority of possible deceased organ donors subject to ICOD develop BD and fulfil the criteria of potential DBD donors during the first 72 hours following the brain injury [24]. In patients who have not deteriorated to BD about 72 hours following admission to ICU, cDCD may be considered and discussed with the relatives.

The use of ICOD in nearly dead patients solely to preserve their organs for transplantation and to optimise the chance for deceased donation may raise some legal and ethical concerns. In general, however, specific legislation for this practice is absent. The practice of ICOD is currently justified by the legal and ethical considerations of fulfilling the patient's overall best interests including the patient's living will and beliefs, not solely their clinical benefit. The main threat to decisions regarding the use of the medical treatment for organ donation in end-of-life situations must be respect for the patient's individual dignity and autonomy by carrying out as far as possible what would have been their wishes if they could express them. The decision-making process regarding medical treatment and the use of some inva-

Figure 2.2. **Proposed pathway for clinical decisions on initiation of intensive care to facilitate organ donation and elective non-therapeutic ventilation**



* cDCD: controlled donation after circulatory death, only if it is allowed by national legislation.

BD: brain death; DC: donor co-ordinator; DCD: donation after circulatory death; ENTV: elective non-therapeutic ventilation; ICOD: intensive care to facilitate organ donation; ICU: intensive care unit; OPO: organ procurement organisation; RAW: registry of anticipated willingness; WLST: withdrawal of life-sustaining treatments.

sive clinical procedures in these circumstances both have to meet the requirements of internationally acknowledged ethical principles, namely autonomy, beneficence, non-maleficence and justice [5]. Moreover, admission of a critically ill patient with DBI to the ICU provides the best opportunity for end-of-life and palliative care, it allows time to establish a safer prognosis and it gives the family the time to adapt to a tragic and unexpected event [31].

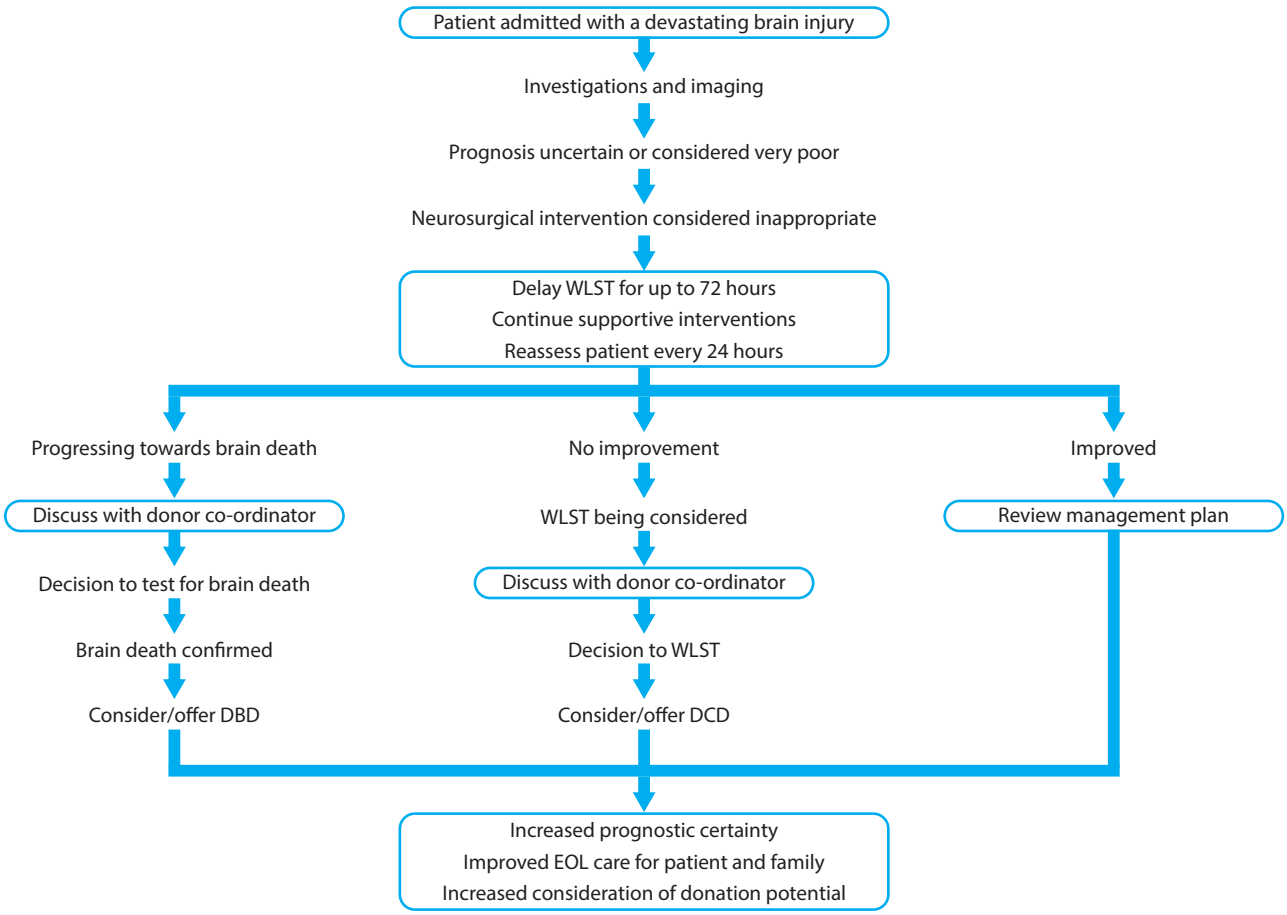
From the perspective of using ICU resources for non-curative purposes, the fast deterioration to BD in the majority of patients with DBI means that ICOD does not place unacceptable pressures on ICU capacity. The admission of a dying patient with DBI to the ICU, when end-of-life care and organ donation are being considered, is acceptable due to appreciable community benefit, yielding an average of over seven times in the quality-adjusted life-years (7.3 QALYs) per ICU bed-day compared with the average benefit for ICU patients expected to survive [32]. The family distress caused by the high risk of impending death of their loved one and the application of invasive non-therapeutic interventions can be mitigated by the awareness that this procedure is necessary to meet the desire of their family member and that it might save other lives owing to the organ donation.

Another approach is to avoid early decisions on WLST in the emergency department and to admit all intubated patients with a DBI to the ICU with the primary intention of ensuring the safety of the prognostication, which is virtually always in a patient's best interest. These pathways aspire to improve end-of-life care for patients and their families, and also ensure that organ donation is always considered as part of the patient's end-of-life care [31] (see Figure 2.2, Figure 2.3). This approach is similar to, and broadly based upon, that developed for the management of patients with hypoxic brain injury who remain comatose after resuscitation from an out-of-hospital cardiac arrest [33].

2.5. Identification and referral of possible organ donors

Failure to identify and refer organ donors is one of the most important reasons for failure to realise the deceased donation process as described in Figure 2.1 [9]. In the ACCORD project, 35 % of patients

Figure 2.3. **Proposed pathway for clinical decisions on initiation of intensive care to facilitate organ donation and elective non-therapeutic ventilation**

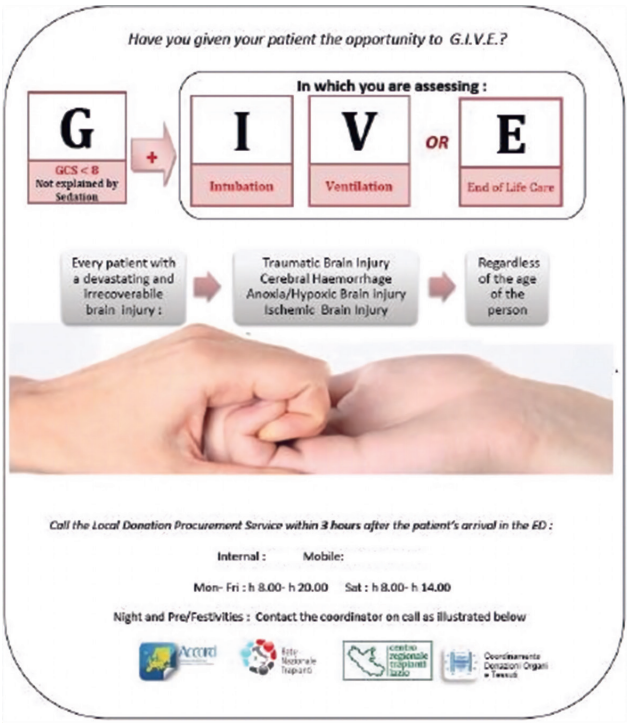


* cDCD: controlled donation after circulatory death, only if it is allowed by national legislation.

DBD: donation after brain death; DCD: donation after circulatory death; EOL: end-of-life; WLST: withdrawal of life-sustaining treatments.

who died as a result of a DBI were never referred to the donor co-ordinator or the staff of the OPO, thus immediately ruling out the possibility of organ donation [13].

Figure 2.4. **Poster containing information for the referral of possible donors from the emergency department to the donor co-ordination team**



Identification by the treating physicians of opportunities for deceased organ donation, and referral of cases to the donor co-ordinator, can occur at different stages of the (previously defined) WHO Critical Pathway for Deceased Donation shown in Figure 2.1. In most European countries there is no consensus on the timing of referral, and nor are there uniform criteria for donor referral. The stage for referral has been defined only in some national guidelines, with significant variation between countries.

However, if legally possible, referral should ideally occur at an early stage, as soon as the possible organ donor is identified. In general terms this is the point at which a patient's death is considered to be inevitable and imminent, and when the objectives of treatment transition from active therapy to palliative and end-of-life care [6]. Referral can also occur based systematically on a poor prognosis of the patient, even if active medical treatment is to be continued. Referral at this point is considered as a notification rather than a formal referral, and allows donor co-ordinators to be aware of cases for planning purposes, but with no immediate action to be necessarily taken by them. Early referral has many advantages. Assessment of medical suitability for organ donation can begin earlier, which may reduce delays for both the ICU and the donor's family. If needed, expert assistance for BD testing or physiological optimisation of the donor can be provided. Early referral also allows better planning of the family approach and prompt identification and resolution of potential coroner/judicial issues.

Whatever the point at which the decision is taken to communicate a case to the donor co-ordinator, referral should be a routine practice. Donor identification and referral should be underpinned by dedicated protocols, developed at national or local level, that specify clinical triggers for referral, education and training of critical-care professionals and quality-control assessment.

2.5.1. Clinical triggers for the identification and referral of deceased organ donors

The specification of clinical triggers in local or national protocols facilitates compliance with the routine referral policy. Clinical triggers take the form of specific clinical criteria which, when met, should result in referral by the treating team. They should be agreed by consensus and developed by an interdisciplinary panel of experts that includes all professionals who care for patients with a DBI (e.g. personnel from ICUs, emergency care departments, neurology and neurosurgery). Clinical triggers should be simple, clearly defined and easy to audit. They should focus on prognostic factors and should lead to referral regardless of a patient's age or co-morbidity, since limiting referral based on age or apparent medical contraindications to donate may lead to a significant number of lost opportunities for organ donation. Clinical triggers should be easily available to critical-care professionals, for example, on simple posters containing the relevant information and located at visible places in critical-care units (see Figure 2.4).

Sections 2.5.1.1 and 2.5.1.2 (below) provide examples of clinical triggers for the referral of DBD and DCD donors. It should be noted that the triggers specified for DBD donors can be also applicable to cDCD donors in cases where the patient with a DBI does not deteriorate to BD and the decision to move to WLST is made.

2.5.1.1. *Clinical triggers for the identification and referral of donors for donation after brain death*

The Glasgow Coma Scale (GCS) is most commonly used to define clinical triggers for referring DBD donors (e.g. GCS < 8). In Croatia, certain scores

of different neurological scales, depending on the aetiology of brain injury, are recommended to trigger notification to the donor co-ordinator:

a. For patients with ischaemic brain injury, a National Institute for Health (UK) stroke severity scale ≥ 27 [34];
b. For patients with cerebral haemorrhage, an intracerebral haemorrhage scale [35] or a Hunt–Hess scale [36] ≥ 4;
c. For patients with secondary cerebral anoxia, central nervous system tumours or infections, or severe cerebral trauma, a GCS ≤ 6.

Patients at this stage may still be receiving active treatment. However, according to Croatian guidelines, those patients should be reported as possible donors to the donor co-ordinator [37] (see Table 2.2). It is of the utmost importance that staff ensure monitoring of brain damage, preferably every hour, and documentation of GCS, size of pupils and reaction to light, brainstem reflexes and spontaneous respiration in the ICU chart – an examination that is in any case a basic standard in ICUs. Patients evolving to a situation consistent with imminent death as defined by de Groot *et al.* must be reported to the donor co-ordinator [18]. Imminent death is defined by a GCS of 3 and the progressive absence of at least three out of six brainstem reflexes or a FOUR score of EoMoBoRo [38].

In the United Kingdom, the National Institute for Health and Care Excellence recommendations for the identification and referral of possible organ donors are based on the principle that organ donation should be a component of end-of-life care planning, and are incorporated into an NHS Blood and Transplant strategy for implementation of these recommendations [40]. In patients with a catastrophic brain injury, referral is recommended in the absence of one or more brainstem reflexes and a GCS ≤ 4, unless there is a clear reason why the above clinical triggers are not met (for example, because of sedation) and/or a decision has been made to perform BD testing, whichever is the earlier.

In the United States, all hospitals are legally required to refer all imminent deaths to the local OPO. 'Required referral' or 'routine notification' represents a unique practice internationally in terms of being mandatory [41]. A patient with imminent BD is defined as a mechanically ventilated, deeply comatose patient, admitted to an ICU, with irreversible catastrophic brain damage of known origin (e.g. traumatic brain injury, subarachnoid or intracranial haemorrhage). Electronic clinical decision systems can be helpful in this setting [42].

There is ongoing research on clinical and radiological factors to predict progression to BD in patients with a DBI in whom the decision has been made not to treat on the ground of futility. Derived new prognostic scores may become clinical triggers for the referral of possible DBD donors and may support physicians in making difficult decisions on ICOD.

In a retrospective analysis of patients with acute stroke and high probability of developing BD in five centres in Lorraine (France), the authors identified six clinical and radiological factors which could form a predictive score of BD in acute phase of severe stroke with high predictive values (score 1 *v.* score 2: 72 *v.* 77 %). The GCS score ≤ 6 before sedation, stroke volume > 65 mL, presence of herniation and/or hydrocephalus on brain imaging, initial systolic blood pressure > 150 mmHg and history of alcohol abuse represent six different predictive factors of poor prognosis and high probability of progression to BD within 24 h following stroke onset. Taken together, these factors can make a simple score system that can help clinicians at emergency departments, neurological wards or stroke units to more accurately assess patients with severe stroke as being possible organ donors and to facilitate discussions with family members about treatment futility and ICOD [43].

Table 2.2. **Clinical triggers for identification and referral of donors for donation after brain death in Croatia**

Clinical triggers	Ischaemic brain injury	Intracerebral haemorrhage	Secondary cerebral anoxia	CNS tumour	CNS infection	Cerebral trauma
Recommended referral	NIHSS ≥ 27	ICHS or Hunt–Hess ≥ 4	GCS ≤ 6			
Required referral	GCS 3 and progressive absence of at least three out of six brain stem reflexes or FOUR score of EoMoBoRo					

Note: CNS: central nervous system; GCS: Glasgow coma scale; ICHS: intracerebral haemorrhage scale; NIHSS: National Institute for Health stroke severity scale.
Sources: [39], [37].

Non-contrast computed tomography (CT) appearance of acute extravasation of blood into a cerebral haematoma (swirl sign) and CT angiographic spot sign visible as unifocal or multifocal contrast enhancement within an acute, primary intracerebral haemorrhage both represent sites of active haemorrhage and are independent predictors of early haematoma expansion and poor outcome in patients with intracerebral haemorrhages [44].

Table 2.3. **ICD-10 codes of diseases associated with potentially devastating cerebral lesions related to brain death**

Group of cerebral lesions	ICD-10 code*
Trauma	S02 Fracture of skull and facial bones
	S06.1 Traumatic cerebral oedema
	S06.2 Diffuse brain injury
	S06.3 Focal brain injury
	S06.4 Extradural haemorrhage
	S06.7 Intracranial haemorrhage with prolonged coma
	S06.8 Other intracranial injuries
	S06.9 Intracranial injury unspecified
Cerebrovascular accidents	I60 Subarachnoid haemorrhage
	I61 Intracranial haemorrhage
	I62 Other non-traumatic intracranial haemorrhage
	I63 Cerebral infarction
	I64 Stroke not specified as stroke or infarction
	I65 Occlusion and stenosis of precerebral arteries
	I66 Occlusion and stenosis of cerebral arteries
Cerebral damage	G93.1 Anoxic brain damage
	G93.5 Compression of brain
	G93.6 Cerebral oedema
Cerebral neoplasm	C71 Malignant neoplasm of the brain
	D33 Benign neoplasm of the brain
CNS infections	G00, G01, G02, G03 Meningitis

* In the case of an ICD code with three digits – e.g. G93.1 – all subclassifications should be included.

Sources: Achieving Comprehensive Coordination in Organ Donation through the European Union–Accord Joint Action [13]; Humbertjean L, Mione G, Fay R *et al.* Predictive factors of brain death in severe stroke patients identified by organ procurement and transplant coordination in Lorraine, France [43].

Some ICD-10 codes are related to potentially devastating cerebral lesions that can lead to BD (see Table 2.3) [45]. Review of this codified data collection (or of the non-codified list of diagnoses of patients at hospital admission or when complications occur) can be used by donor co-ordinators to proactively identify patients at risk of dying as a result of a DBI. Patients with such ICD-10 codes should be monitored. This tool can also be used to evaluate compliance with donor referral, which should be standard practice. In case of non-compliance, the underlying root cause should be identified, and efforts should be made to educate treating physicians in the routine referral policy.

2.5.1.2. *Clinical triggers for the identification and referral of donors for donation after circulatory death*

cDCD and uDCD donors proceed from very different clinical scenarios that require separate and distinct clinical triggers for identification and referral.

The potential for cDCD should be considered in any critically ill patient in whom a decision of WLST is being considered or has been made because treatment is no longer in the best interests of the patient. Most cDCD donors have suffered a DBI similar to DBD donors, but have not deteriorated to BD. It is always important that the treating physician considers if death by neurological criteria might be determined if supportive treatment is maintained and WLST is delayed. It has been estimated that about 30 % of actual cDCD donors in the United Kingdom had the potential to progress to BD and DBD if the WLST had been delayed by 36 hours [46]. DBD should always be considered preferable to cDCD, since DBD yields a higher number and better quality of organs than DCD. There is a percentage of potential cDCD donors in whom the decision to withdraw treatment is made in the context of end-stage respiratory or neuromuscular disease. An undesired replacement of DBD by cDCD is not a possibility in this particular context.

The identification of uDCD donors poses a different set of challenges because of the different organisational and logistical challenges posed, since this type of donation is activated by identification of an unexpected cardiac arrest unresponsive to advanced CPR that may have occurred either in hospital or outside [46]. Activation of the uDCD process requires carefully planned co-operation between teams in charge of CPR (emergency and ICU) and the donor co-ordination team. Dedicated protocols also specify different selection criteria. Potential uDCD donors should be medically suitable, based on similar criteria to those applied in the DBD setting. In addition, some other specific selection criteria must be met and there are limits to the time extending from the cardiac arrest to the initiation of preservation measures (warm ischaemia time).

Recommendations for the identification and referral of potential uDCD donors have been developed in most countries where uDCD is standard

practice [47][48][49]. More detailed information is provided in Chapter 12.

2.5.2. Training and education

An effective system for the routine identification and referral of organ donors requires close co-operation between healthcare professionals caring for critically ill patients (personnel from ICUs, the emergency department, neurology and neurosurgery community) and the donor co-ordination team or OPO staff. Continuous education and training of these professional groups on the identification of possible organ donors and their timely referral is of utmost importance and supports the dissemination of basic concepts about organ donation. Donor co-ordinators must actively ensure and help to deliver this continuous education and training through various means that must include dedicated courses on a regular basis.

The target of these courses should be all medical and non-medical staff from intensive and

Table 2.4. **ODEQUS quality criteria on donor identification and referral [54]**

Donation after brain death	Donation after circulatory death
Each hospital should implement a systematic approach to evaluate the possibility for organ donation in every end-of-life care pathway.	Each hospital should implement a systematic approach to evaluate the possibility for organ donation in every end-of-life care pathway.
Written definition of 'possible donor' is available and known by personnel of the units of the hospitals where possible donors may be found.	Written definition of 'possible donor' is available and known by personnel of the units of the hospitals where possible donors may be found.
A possible donor is always referred to the donation team irrespective of the patient's medical condition (age, past medical history etc.).	A possible donor is always referred to the donation team irrespective of the patient's medical condition (age, past medical history etc.).
	In all potential donors, the timing of treatment withdrawal should be delayed until the different donation opportunities have been considered by the donation team.
The clinical responsibilities and specific targets of the physicians of each ICU and ED should include possible donor identification.	The clinical responsibilities and specific targets of the physicians of each ICU and ED should include possible donor identification.
	Each hospital that has an out-of-hospital uDCD programme should have an updated collaborative protocol with emergency services outside the hospital in order to establish criteria for the identification of potential DCD donors.
All patients identified as possible donors should be referred to the donation team and homeostasis maintained, facilitating early brain death diagnosis as soon as the clinical criteria to test are met.	
Donation team monitors the progression of each possible donor admitted in the ICU on a daily basis.	
	In all potential uDCD donors, the asystolic time before CPR is initiated by the Emergency Service should be shorter than the predetermined time (specified in the protocol) after cardiac arrest has occurred.
	All patients with irreversible cardiocirculatory arrest, no medical contraindication for organ donation and a warm ischaemia time that is short enough to allow for the extraction of organs suitable for transplant should be considered potential uDCD donors.
	Each hospital that has an in-house uDCD programme should have an updated protocol, which should be known by all healthcare professionals working in the hospital, in order to establish criteria for the identification of potential DCD donors.
	Each hospital that has a cDCD programme should have an updated protocol, which should be known by all healthcare professionals working in critical care settings and transplant team members, in order to establish criteria for identification of patients who can potentially be eligible for DCD.
	All potential DCD donors should be reported to the donation team as soon as the decision to withdraw treatment is made.

Note: cDCD: controlled donation after circulatory death; DBD: donation after brain death; ED: emergency department; ICU: intensive care unit; uDCD: uncontrolled donation after circulatory death.

emergency care units and from other units caring for patients with DBI and other critically ill patients. The type and duration of these training courses, as well as the frequency of attendance, are to be agreed upon at hospital/regional/national level. Training courses can be organised at national level through national programmes or at international level through international educational programmes, courses, exams and certification initiatives. It is recognised that the training of healthcare professionals involved in deceased organ donation has a positive impact on the effectiveness of the deceased donation process, improving the functioning of local and national transplant systems [50].

2.5.3. Quality system

As part of the quality-control system (see Chapter 17), a proactive donor-referral programme must be developed at national, regional or local level and implemented at each hospital where there is a potential for organ donation. This quality-control system requires the development of dedicated protocols on donor referral targeted at all those professionals attending to critically ill patients.

The EU-funded project ODEQUS (Organ Donation European Quality System) was designed as a tool for quality systems in the donation process. The project counted on the participation of health authorities and hospitals from 16 European countries. It described detailed quality criteria and quality indicators for both types of deceased organ donor, DBD and DCD [51]. These quality criteria and indicators were proposed with the aim of evaluating performance of procurement hospitals in all steps of the deceased donation process. Indicators were developed to allow comparison of performance between different hospitals. Several of these quality criteria and indicators were particularly focused on the critical step of donor identification and referral. Quality criteria for donor identification and referral developed in the ODEQUS project are depicted in Table 2.4. Both DBD and DCD pathways can be addressed through these indicators to identify specific areas in the deceased donation process that can be improved at hospital level.

A quality system for donation processes should be developed at all procurement hospitals as well as at national level. Regular audits should be conducted at each donor hospital. Accurate audit of practices is a prerequisite of any attempt to improve organ donation. It allows assessment of the potential for organ donation, evaluation of performance in the deceased donation process and identification of areas for improvement. Ongoing data collection at local, regional and national levels is a prominent feature of successful donation programmes.

Regular audits should include internal audits (performed by in-house staff) and external audits (performed by external experts) to identify and learn from missed opportunities for organ donation [52]. Results of these audits should be analysed regularly and at least annually. The quality system at national level should include an analysis of performance of all hospitals with the potential for organ donation. This should contribute to identifying the weakest points in the organ donation process and to applying appropriate measures for improving performance.

The starting point in auditing deceased donation is variable. Existing national data collections consist of a clinical chart review of deaths occurring at the ICU and/or the emergency department of procurement hospitals to then identify potential DBD donors and, if appropriate, potential cDCD donors [17][53][54]. But the clinical chart review can be extended to deaths occurring at any hospital unit beyond the ICU. This activity can be facilitated by focusing on deaths likely to have been caused by a DBI, particularly those conditions that are known to be common causes of BD. For administrative purposes, nearly all hospitals use ICD-10 coding linked to other patients' data during hospital stays. It is helpful to use such pre-existing administrative data collections provided by the IT system via the admission department for simplified and targeted clinical chart reviews and/or quality analysis. Table 2.3 includes a list of ICD-10 codes potentially associated with devastating cerebral lesions.

Identifying potential DBD donors based on data available in a clinical chart must be performed in a uniform and consistent manner – the corresponding criteria used in the Spanish Quality Assurance Programme are described in Appendix 3 [17]. Once potential donors are identified through the clinical chart review, information should be collected and documented on the reason for non-referral, if appropriate. In every case, additional reasons why potential donors were not converted into actual donors should also be addressed.

2.6. Conclusion

Unless an active donor identification and referral programme is established at each procurement hospital, opportunities for deceased organ donation will continue to be lost. Failure to identify possible organ donors is the most important reason explaining differences in deceased donation rates across jurisdictions. Dedicated protocols with specified

clinical triggers to facilitate donor identification and referral must be established at each hospital. Donor co-ordinators will play a key role in ensuring the quality of these protocols. Efforts should be made to ensure education and training of all healthcare professionals who care for patients with a DBI, especially in ICUs, emergency departments and neurology/neurosurgery departments.

The principle that organ donation must be a component of end-of-life care should underpin the practice of routine referral by critical-care physicians. Their primary duty when caring for patients with a DBI is to preserve life. However, when the patient has deteriorated to a BD condition or when the futility of further treatment has been recognised, the duties of critical-care physicians shift from active treatment to palliative and end-of-life care. Approaches that regard organ donation as a component of end-of-life care allow physicians to make this transition without fear of being conflicted. The emergence of such philosophies will continue to require the adaptation of existing legal frameworks and professional and public debate in most countries.

Research agenda

From the literature and discussion of the available evidence, several topics have been identified for which evidence is inconsistent, insufficient or non-existent. The authors of this guide recommend that future research, where possible in well-designed randomised clinical trials, should focus on the following research gaps:

1 Relevance of emergency departments in the identification of donation opportunities.
2 Use of electronic tools that can extract relevant data from medical history to trigger donor identification.
3 Identification of barriers to identifying donation opportunities and referring possible organ donors, particularly from the perspective of critical-care professionals.
4 Specificity and sensitivity of triggers for referral: Do they identify all possible donors? Do they identify many patients who have no potential to become actual donors? Do they increase the workload of donor co-ordinators?
5 Appropriate timing for donor referral (before reaching decisions on WLST or decisions to test).

2.7. References

1. World Health Organization (WHO), Transplantation Society (TTS) and Organización Nacional de Transplantes (ONT). Third WHO Global Consultation on Organ Donation and Transplantation: striving to achieve self-sufficiency, 23-25 March 2010, Madrid, Spain. *Transplantation* 2011;91(Suppl 1):S27-8. https://doi.org/10.1097/TP.0b013e3182190b29.
2. Global Observatory on Organ Donation and Transplantation, available at www.transplant-observatory.org, accessed 17 May 2021.
3. Domínguez-Gil B, Haase-Kromwijk B, Van Leiden H *et al.* Current situation of donation after circulatory death in European countries. *Transpl Int* 2011, 24(7), 676-86, https://doi.org/10.1111/j.1432-2277.2011.01257.x.
4. Domínguez-Gil B, Delmonico FL, Shaheen FAM *et al.* The critical pathway for deceased donation: reportable uniformity in the approach to deceased donation. *Transpl Int* 2011, 24(4), 373-8, https://doi.org/10.1111/j.1432-2277.2011.01243.x.
5. Committee on Bioethics (DH BIO) of the Council of Europe. Guide on the decision-making process regarding medical treatment in end-of-life situations, available at www.coe.int/en/web/bioethics/guide-on-the-decision-making-process-regarding-medical-treatment-in-end-of-life-situations, accessed 17 May 2021.
6. Domínguez-Gil B, Murphy P, Procaccio F. Ten changes that could improve organ donation in the intensive care unit. *Intensive Care Med* 2016, 42(2), 264-7, https://doi.org/10.1007/s00134-015-3833-y.
7. Truog RD, Campbell ML, Curtis JR. American Academy of Critical Care Medicine recommendations for end-of-life care in the intensive care unit: a consensus statement by the American College [corrected] of Critical Care Medicine. *Crit Care Med* 2008, 36(3), 953-63, https://doi.org/10.1097/CCM.0B013E3181659096.
8. Hernández-Tejedor A, Peñuelas O, Sirgo Rodríguez G *et al.* Recommendations of the working groups from the Spanish Society of Intensive and Critical Care Medicine and Coronary Units (SEMICYUC) for the management of adult critically ill patients. *Med Intensiva* 41(5), 285-305, https://doi.org/10.1016/j.medin.2017.03.004.
9. Roels L, Smits J, Cohen B. Potential for deceased donation not optimally exploited: donor action data from six countries. *Transplantation* 2012, 94(11), 1167-71, https://doi.org/10.1097/TP.0b013e31826dde40.
10. Kootstra G, Daemen JH, Oomen AP. Categories of non-heart-beating donors. *Transplant Proc* 1995, 27, 2893-4.
11. Thuong M, Ruiz A, Evrard P *et al.* New classification of donation after circulatory death donors definitions and terminology. *Transpl Int* 2016, 29(7), 749-59, https://doi.org/10.1111/tri.12776.
12. Lomero M, Gardiner D, Coll E *et al.* Donation after circulatory death today: an updated overview of the European landscape. *Transpl Int* 2020, 33(1), 76-88, https://doi.org/10.1111/tri.13506.

13. ACCORD: Achieving Comprehensive Coordination in Organ Donation throughout the European Union – Results 2015, available (including link to Accord home page) at www.era-edta.org/ekha/ACCORD_Joint_Action_on_Organ_Donation_Results.html, accessed 31 May 2021.
14. Sprung CL, Ricou B, Hartog CS *et al.* Changes in end-of-life practices in European intensive care units from 1999 to 2016. *JAMA* 2019, 322(17), 1692-1704, https://doi.org/10.1001/jama.2019.14608.
15. de Groot YJ, Wijdicks EFM, van der Jagt M *et al.* Donor conversion rates depend on the assessment tools used in the evaluation of potential organ donors. *Intensive Care Med* 2011, 37(4), 665-70, https://doi.org/10.1007/s00134-011-2131-6.
16. Manara AR, Murphy PG, O'Callaghan G. Donation after circulatory death. *Br J Anaesth* 2012, 108 Suppl, i108-21, https://doi.org/10.1093/bja/aer357.
17. de la Rosa G, Domínguez-Gil B, Matesanz R *et al.* Continuously evaluating performance in deceased donation: the Spanish quality assurance program. *Am J Transplant* 2012, 12(9), 2507-13, https://doi.org/10.1111/j.1600-6143.2012.04138.x.
18. de Groot YJ, Jansen NE, Bakker J *et al.* Imminent brain death: point of departure for potential heart-beating organ donor recognition. *Intensive Care Med* 2010, 36(9), 1488-94, https://doi.org/10.1007/s00134-010-1848-y.
19. Domínguez-Gil B, Coll E, Pont T *et al.* End-of-life practices in patients with devastating brain injury in Spain: implications for organ donation. *Med Intensiva* 2017, 41(3), 162-73, https://doi.org/10.1016/j.medin.2016.07.011.
20. Martín-Loeches I, Sandiumenge A, Charpentier J. Management of donation after brain death (DBD) in the ICU: the potential donor is identified, what's next? *Intensive Care Med* 2019, 45(3), 322-30.
21. Escudero D, Otero J, Menéndez de León B *et al.* Organ donation and elective ventilation: a necessary strategy. *Biomed Res Int* 2017, 15 January 2017, 1-6, https://doi.org/10.1155/2017/7518375.
22. Monette M. The ethics of elective ventilation. *Can Med Assoc J* 2012, 184(16), E841-2, https://doi.org/10.1503/cmaj.109-4261.
23. NSW Health. Discussion paper: the use of *ante mortem* (before death) interventions for organ donation in NSW 2016, available at www.health.nsw.gov.au/legislation/Documents/discussion-paper-organ-donation.pdf, accessed 17 May 2021.
24. Domínguez-Gil B, Coll E, Elizalde J *et al.* Expanding the donor pool through intensive care to facilitate organ donation. *Transplantation* 2017, 101(8), e265-72, https://doi.org/10.1097/TP.0000000000001701.
25. Escudero Augusto D, Martínez Soba F, de la Calle B *et al.* Cuidados intensivos orientados a la donación de órganos. Recomendaciones ONT-SEMICYUC. *Med Intensiva* 2019, 45(4), https://doi.org/10.1016/j.medin.2019.09.018.
26. Martín-Delgado MC, Martínez-Soba F, Masnou N *et al.* Summary of Spanish recommendations on intensive care to facilitate organ donation. *Am J Transplant* 2019, 19(6), 1782-91, https://doi.org/10.1111/ajt.15253.
27. Sandiumenge A, Ramírez-Estrada S, Mazo C *et al.* Donor referral from outside the intensive care unit: A multidisciplinary cooperation model using communication apps and redefining refereal criteria. *Med Intensiva* 2018, 44(3), 142-9, https://doi.org/10.1016/j.medin.2018.08.009.
28. Martínez Soba F, Pérez Villares JM, Martínez-Camarero L *et al.* Intensive care to facilitate organ donation: a report on the experience of 2 Spanish centers with a common protocol. *Transplantation* 2019, 103(3), 558-64, https://doi.org/10.1097/TP.0000000000002294.
29. Mazo C, Gómez A, Sandiumenge A *et al.* Intensive care to facilitate organ donation: a report on the 4-year experience of a Spanish center with a multidisciplinary model to promote referrals out of the intensive care unit. *Transplant Proc* 2019, 51(9), 3018-26, https://doi.org/10.1016/j.transproceed.2019.08.025.
30. Souter MJ, Blissitt PA, Blosser S *et al.* Recommendations for the critical care management of devastating brain injury: prognostication, psychosocial, and ethical management: a position statement for healthcare professionals from the Neurocritical Care Society. *Neurocrit Care* 2015, 23(1), 4-13, https://doi.org/10.1007/s12028-015-0137-6.
31. Manara AR, Thomas I, Harding R. A case for stopping the early withdrawal of life sustaining therapies in patients with devastating brain injuries. *J Intensive Care Soc* 2016, 17(4), 295-301, https://doi.org/10.1177/1751143716647980.
32. Nunnink L, Cook DA. Palliative ICU beds for potential organ donors: an effective use of resources based on quality-adjusted life-years gained. *Crit Care Resusc* 2016, 18(1), 37-42.
33. Manara AR, Menon DK. Withdrawal of treatment after devastating brain injury: post-cardiac arrest pathways lead in best practice. *Anaesthesia* 2017, 72(10), 1179-84, https://doi.org/10.1111/anae.13966.
34. Brott T, Adams HP, Olinger CP *et al.* Measurements of acute cerebral infarction: a clinical examination scale. *Stroke* 1989, 20, 864-70, https://doi.org/10.1161/01.STR.20.7.864.
35. Hemphill JC, Bonovich DC, Besmertis L *et al.* The ICH score: a simple, reliable grading scale for intracerebral hemorrhage. *Stroke* 2001, 32, 891-7, https://doi.org/10.1161/01.str.32.4.891.
36. Hunt WE, Hess RM. Surgical risk as related to time of

intervention in the repair of intracranial aneurysms. *J Neurosurg* 1968, 28(1), 14-20, https://doi.org/10.3171/jns.1968.28.1.0014.

37. Živčić-Ćosić S, Bušić M, Župan Ž *et al.* Development of the Croatian model of organ donation and transplantation. *Croat Med J* 2013, 54(1), 65-70, https://doi.org/10.3325/cmj.2013.54.65.
38. Wijdicks EFM, Bamlet WR, Maramattom BV *et al.* Validation of a new coma scale: The FOUR score. *Ann Neurol* 2005, 58(4), 585-93, https://doi.org/10.1002/ana.20611.
39. Župan Ž. The proposed 2011-2016 national strategy for timely and optimal management of organ and tissue donors, *Medix* 2011;17(92/93):149-55.
40. National Institute for Health and Clinical Excellence (December 2011, updated December 2016). Organ donation for transplantation: improving donor identification and consent rates for deceased organ donation, available at www.nice.org.uk/guidance/CG135, accessed 17 May 2021.
41. Nathan HM, Conrad SL, Held PJ *et al.* Organ donation in the United States. *Am J Transplant* 2003, 3 (Suppl 4), 29-40, https://doi.org/10.1034/j.1600-6143.3.s4.4.x.
42. Zier JL, Spaulding AB, Finch M *et al.* Improved time to notification of impending brain death and increased organ donation using an electronic clinical decision support system. *Am J Transplant* 2017, 17(8), 2186-91, https://doi.org/10.1111/ajt.14312.
43. Humbertjean L, Mione G, Fay R *et al.* Predictive factors of brain death in severe stroke patients identified by organ procurement and transplant coordination in Lorraine, France. *Transpl Int* 2016, 29(3), 299-306, https://doi.org/10.1111/tri.12695.
44. Demchuk AM, Dowlatshahi D, Rodríguez-Luna D *et al.* Prediction of haematoma growth and outcome in patients with intracerebral haemorrhage using the CT-angiography spot sign (PREDICT): a prospective observational study. *Lancet Neurol* 2012, 11(4), 307-14, https://doi.org/10.1016/S1474-4422(12)70038-8.
45. Matesanz R, Domínguez-Gil B, Marazuela R *et al.* Benchmarking in organ donation after brain death in Spain. *Lancet* 2012, 380(9842), 649-50, https://doi.org/10.1016/S0140-6736(12)61371-3.
46. Consensus statement on donation after circulatory death from the British Transplantation Society and Intensive Care Society [available at www.odt.nhs.uk/deceased-donation/best-practice-guidance/donation-after-circulatory-death/ under 'Professional guidance', accessed 15 May 2021.
47. Organización Nacional de Trasplantes, Donation after circulatory death in Spain: current situation and recommendations. National consensus document 2012 (in Spanish), available at www.ont.es/infesp/Paginas/DocumentosdeConsenso.aspx, accessed 17 May 2021.
48. Shemie SD, Baker AJ, Knoll G *et al.* Donation after cardiocirculatory death in Canada. *Can Med Assoc J* 2006, 175(8), S1, https://doi.org/10.1503/cmaj.060895.
49. Bernat JL, D'Alessandro AM, Port FK *et al.* Report of a national conference on donation after cardiac death. *Am J Transplant* 2006, 6(2), 281-91, https://doi.org/10.1111/j.1600-6143.2005.01194.x.
50. Manyalich M, Guasch X, Gómez MP *et al.* Organ Donation European Quality System: Odequs Project Methodology. *Transplant Proc* 2013, 45(10), 3462-5, https://doi.org/10.1016/j.transproceed.2013.09.009.
51. Odequs project website, available at www.odequs.eu, accessed 17 May 2021.
52. Dopki Guidelines for quality programmes in organ donation, available at www.ont.es/internacional/Documents/dopki.pdf, accessed 17 May 2021.
53. Barber K, Falvey S, Hamilton C *et al.* Potential for organ donation in the United Kingdom: audit of intensive care records. *BMJ* 2006, 332(7550), 1124-7, https://doi.org/10.1136/bmj.38804.658183.55.
54. Wesslau C, Grosse K, Krüger R *et al.* How large is the organ donor potential in Germany? Results of an analysis of data collected on deceased with primary and secondary brain damage in intensive care unit from 2002 to 2005. *Transpl Int* 2007, 20(2), 147-55, https://doi.org/10.1111/j.1432-2277.2006.00413.x.

Related document

Appendix 3. Criteria for the identification of potential donors after brain death in a retrospective clinical chart review (Spain)

Chapter 3. Determination of death by neurologic criteria

3.1. Introduction

Since their publication in August 1968, the Harvard Committee report and the Sydney Declaration of the 22nd World Medical Assembly have led to a new model for diagnosing human death, based on neurologic criteria [1, 2]. A decade previously, in 1957, the allocution of Pope Pius XII, *The prolongation of life*, pointed out the possibility – with the help of new artificial processes, such as mechanical ventilation – of artificially keeping a person 'alive' after the brain has ceased to function.

The focus of attention shifted from the condition of the heart to the state of the brain as a consequence of the introduction of artificial ventilation in the polio epidemics of the early 1950s in Europe [3]. As a result, many European investigators observed, and later on concluded, that irreversible failure of brain functions is equivalent to death after proper confirmation and they considered discontinuing further therapy [2]. Two landmark accounts appeared in 1959 when, studying comatose and apnoeic patients, Wertheimer and Jouvet described the 'death of the nervous system' [4] and Mollaret and Goulon coined the term *coma dépassé,* translated as 'beyond coma' or 'ultra-coma' and subsequently by others as 'irreversible coma' [5]. These patients had lost consciousness, brainstem reflexes and respiration, and their electro-encephalograms were permanently flat. The investigators' conclusion was that the brains of these patients were irreversibly dysfunctional and that it was justifiable to disconnect them from the respirator.

The subsequent development of organ and tissue transplantation, initially in the fields of kidney, heart and cornea transplantations, provoked discussion on the neurologic determination of human death. At present, the complete and irreversible failure of central nervous system (CNS) functions constitutes the authentic frontier between life and death of human beings. However, not all medical schools accept the same concept of brain death (BD). Consequently, the criteria for diagnosis are different according the concept of brain death used. The 'whole-brain death' concept is the most widespread one, and it is characterised by the irreversible cessation of hemispheric and brainstem neurological functions [1]. In 1976, the Conference of Medical Royal Colleges and their Faculties in the United Kingdom published a statement on the diagnosis of BD defined as the 'complete, irreversible loss of brainstem function', which pointed to the brainstem as the centre of brain function (brainstem death) [6].

This 'brainstem death' concept (in place of the concept of 'whole-brain death') explains why, in some countries, complementary tests are not legally required for the confirmation of clinical BD diagnosis, based upon cessation of brainstem function. However, they can be performed as an ancillary study to assist the clinician in specific situations (neurodepressive agents, metabolic disorder, facial or brainstem damage, infants and children).

The diagnosis of BD typically takes place in intensive care units (ICUs) or in emergency departments. It demands the presence of properly qualified, trained and competent personnel and appropriate facilities and equipment. To ensure that a BD dec-

laration is beyond reproach, it needs a complete and comprehensive clinical evaluation performed by trained physicians. This should be based on scientific, nationally agreed criteria, with rigorous protocols for the complementary tests used, and should acknowledge that the determination of death and the time of declaration of death stay under the legal responsibility of the physician in charge of the dead patient.

Nowadays in Europe, donation after brain death (DBD) donors represent the principal source of transplantable organs and tissues, ahead of donation after the circulatory determination of death (DCD) donors or living donors.

The purpose of this chapter is to provide some guidance on BD diagnosis according to the best practices usually applied at European level, knowing that important differences still exist between countries concerning legal frameworks or national recommendations on criteria for BD diagnosis. Specific differences in physical examination, ancillary studies and number of examinations may vary for children and are discussed in section 3.6. For this reason, each donor co-ordinator, as well as any physician qualified to perform BD diagnosis, must be familiar with the national formal rules in their home country, ensuring strict adherence to these rules on the basis of legal texts or official guidelines.

3.2. Epidemiology and aetiology of brain death

Up to 15 % of adult patients dying in European ICUs can be expected to present with a clinical condition consistent with BD [7]. Other data collected in European countries (in particular, Germany) suggest that 50-65 % of all deaths with an acute primary or secondary cerebral lesion (ACLDs) in an ICU (traumatic brain injury, haemorrhagic and ischaemic stroke, subarachnoid haemorrhage, meningitis, encephalitis, CNS neoplasia, anoxia, toxic and poisoning cerebral lesions) may fulfil BD criteria [8].

As only mechanically ventilated patients with acute cerebral lesions may eventually deteriorate and be evaluated for BD, the number of ACLDs in ICUs represents the maximum of brain-dead persons and hence of potential DBD donors. Consequently, the number of ACLDs in ICUs per million population is a useful parameter for evaluating and comparing BD potential. Subsequently, ACLDs can be split by aetiology to monitor in detail the clinical epidemiology of possible organ donors in different countries, regions and centres.

The aetiology of the devastating lesion leading to death may *per se* affect the probability of developing BD. In particular, traumatic brain injury and intracranial bleeding are the two acute cerebral lesions most frequently linked with BD declaration. A smaller proportion of patients with another aetiology of primary or secondary acute cerebral damage, e.g. anoxia, infection or neoplasia, may deteriorate to BD. Case reports of BD declaration followed by successful DBD have been published, in which cerebral catastrophic events were due to poisoning by methanol, tricyclic anti-depressants, insulin, carbon monoxide, ecstasy and other toxins [9].

It is feasible that death from traumatic non-controlled intracranial pressure may be less frequent in young patients than in the past [10]. Moreover, in recent decades the number of severe head injuries related to high-speed road traffic accidents has dramatically decreased in European countries, where strict preventive rules have been implemented. Globally, fatalities from road traffic accidents decreased by 50 % in a decade in Europe (from 54 950 in 2001 to 28 000 in 2012), but eastern European countries still exhibit high traumatic mortality rates – around 80-100 per million population *v.* 30-60 per million in France, Germany, Spain, Italy or the United Kingdom. Around 25 % of traumatic deaths occur in patients over 65 years of age. Thus, donation after traumatic BD is no longer the mainstay for organ donation in most European countries, where stroke is now the leading cause of BD and DBD. In addition, stroke mortality is decreasing, whereas the ageing European population will continue to increase the absolute number of cases. European mortality rates are also higher in eastern countries compared to northern and western countries, with substantially more deaths in both sexes and among younger individuals [11]. Moreover, lower-income countries with weak healthcare systems could exhibit a persistent increase in mortality over time, particularly if control of some risk factors – mainly arterial hypertension or diabetes mellitus – is not achieved.

In practice, the increasing age of utilised DBD donors who died by stroke strongly suggests that potential donors with these clinical findings should be considered as medically suitable for donation.

On the other hand, deaths caused by stroke (ischaemic or haemorrhagic) in elderly persons mainly occur outside the ICU. The possibility of admission to an ICU when treatment is deemed futile may serve to allow ventilation during progression towards BD (so-called 'elective non-therapeutic ventilation'). This option may constitute a challenge for ICUs with limited resources for acute treatable patients. At the same time, the patient's overall best interests in end-of-life choices and the social value of donation have

to be weighed. Elective non-therapeutic ventilation for stroke patients who could progress to BD could reasonably be an important area for increasing organ donation over the next few years and thus could be recognised as an indication for ICU admission (see Chapter 2).

The progression towards BD requires the active support of ventilation and circulatory function in the dying patient in the ICU for hours or days. In practice, the ratio between DBD and DCD donors following the withdrawal of life-sustaining therapy (WLST) is very different between countries in Europe and has changed between 1999 and 2015. Sprung *et al.* published a prospective observational study of 1785 patients who had limitations in life-prolonging therapies or died in 22 European ICUs in 2015-2016, compared with data previously reported from the same ICUs in 1999-2000. Globally, the incidence of BD diagnosis decreased from 9.3 % to 4.1 %. Decisions about withholding or withdrawing of life-prolonging therapy increased respectively from 40.7 % to 50 % and 24.8 % to 38.8 % with differences between centres [11].

Given that DCD is increasingly frequent, there is a risk to shifting from DBD to DCD. In view of the different existing models of end-of-life care across Europe, there may be the potential to adapt such models in a way that is consistent with optimum care of the patient while preserving the possibility of organ donation [12].

DBD potential depends on the epidemiology of acute cerebral lesions in ICUs and end-of-life care of patients with devastating brain lesions. Both may vary greatly across European countries as well as across regions and centres within the same country. Nowadays, the epidemiology of BD strongly depends on the absolute number and the ratio between severe brain injuries and strokes (ischaemic or haemorrhagic) admitted to the ICU, with logistic limitations due to critical-care facilities and emergency systems. Critical-care bed numbers vary considerably between European countries: while the total of ICU beds is 73 500 (11.5 per 100 000 of population), a wide range exists, with 33.7 per 100 000 in Germany and 9.1 per 100 000 in Portugal [13]. Thus, it is likely that healthcare systems have a major impact on the utilisation of these resources and possibly on admission and discharge criteria of patients with devastating cerebral lesions to the ICU. Nevertheless, organ donation is not strictly related to the absolute number of ICU beds, as proved by Portugal with one of the best donation rates in Europe. Consequently, considering the wide differences across countries in the number of severe head injuries, life expectancy, ICU bed resources, ethical principles for end-of-life management and admission policy to ICUs for elderly patients with stroke, BD potential in Europe cannot be considered homogeneous and should be monitored in each country and compared with the absolute number, aetiology and age of ACLDs in each ICU.

Globally, the levels of actual organ donation achieved in ICUs nowadays still fail to match the potential, essentially because of a failure to identify all patients who may fulfil BD criteria. The analysis of this step is the main target of quality programmes adopted in many countries; in particular, the Dopki project compared the monitoring systems in European countries with a view to defining efficiency indicators in the DBD process [7]. A simple and effective method for obtaining retrospective but objective data is the standard use of ICD-10 codes (see Chapter 2) identifying acute cerebral pathologies; the same ICD codes can be used for detecting and monitoring all deaths with acute cerebral lesions outside the ICU, which may represent a good proxy for hospital-possible DBD donors [14]. Prospective national registries including all deaths with acute cerebral lesions, inside and outside the ICU, could be useful for calculating the potentiality of BD detection as well as for monitoring aetiologies and age of potential DBD donors (see Chapter 2).

In the dying patient, the precise definition of an established aetiology capable of causing BD is a prerequisite for using neurologic criteria in determining the irreversibility of the cerebral damage and excluding any possible pitfalls and reversible confounding factor in BD diagnosis. Consequently an investigation and imaging aimed at a precise definition of the aetiology should always be performed. In particular, knowledge of the cause of brain damage and evaluation of its severity and consistency with the development of BD should be clearly requested by any national guidelines concerning the determination of BD.

3.3. Brain death worldwide

Protocols for determining death by neurological criteria vary between countries as recently made evident by Lewis *et al.* [15]. Of 136 analysed countries, 61 % had protocols for determination of death by neurologic criteria, but with some differences (clinical criteria, observation period, use of ancillary test). The authors recommend that a worldwide consensus be reached.

Recently, great work has been done by more than 50 international medical professionals in publishing a worldwide recommendation document

about the determination of BD [16]. The authors decided not to use standard grading of recommendations because of the lack of high quality randomised studies in the field. Thus, many recommendations are based on the consensus and endorsement of five world federations. These recommendations describe the minimal standard for the determination of BD.

Importantly, in this article, the experts explained the concept of brain death and death by neurologic criteria (BD/DNC). It is defined as the complete and permanent loss of brain function as defined by an unresponsive coma with loss of capacity for consciousness, brainstem reflexes and the ability to breathe independently. This may result from the permanent cessation of oxygenated circulation to the brain and/or after a devastating brain injury. Persistence of cellular level neuronal and neuroendocrine activity does not preclude the determi-

Table 3.1. **Key points for the clinical diagnosis of brain death**

Prerequisites for clinical determination of brain death

- Coma of known aetiology and an irreversible condition compatible with BD
- Exclusion of medical conditions that could influence clinical examination (severe disturbances in electrolytes, acid-base or endocrine metabolism)
- Exclusion of central nervous system-depressant drugs: administration/intoxication
- Exclusion of neuromuscular blocking agents
- Core temperature > 35 °C (see §3.4.1.2.a)

Three mandatory clinical signs

- Glasgow Coma score 3
- Absence of brainstem reflexes
- Absence of spontaneous breathing – apnoea test

1. Glasgow Coma score 3

- Hypotonic and nonreactive coma: absence of cerebral motor response to pain stimuli in body parts innervated by cranial nerves (e.g. sustained pressure on temporomandibular joint or supraorbital region), although spontaneous medullary reflexes might still be present.

2. Absence of brainstem reflexes

- During progression to BD, the loss of brainstem reflexes follows a rostro-caudal direction, from the midbrain (mesencephalon) to the pons and, at the end, the medulla (oblongata).
- No pupil reactivity: lack of photo-reactivity, with no response to bright light of the fixed pupils (pupil diameter 4 to 9 mm).
- No eye movement, no movement of eyeballs, lack of oculocephalic/oculovestibular reflex after stimulation by:
  – rapid movement of the head (oculocephalic), tested in the absence of spinal injury,
  – cold caloric manoeuvre (oculovestibular – if tympanum integrity): irrigation of each tympanum with 50 mL of cold water (1 min delay after injection and 5 min interval between the irrigation of the two ears).
- Corneal reflex loss (avoid cornea damage): no palpebral movement after a drop of saline or no palpebral movement when touching cornea edge using a sterile compress carefully.
- No cardiac response after oculo-cardiac reflex (mandatory only in some countries).
- No cough at bronchial suctioning, lack of pharyngeal and tracheal reflexes (mandatory only in some countries).
- Lack of heart rate response after 0.04 mg/kg IV infusion of atropine (mandatory only in some countries).

3. Apnoea test

- Lack of spontaneous breathing due to the loss of respiratory centre function (medulla oblongata).

'Traditional' procedure for apnoea test

– Pre-oxygenation requirement under FiO_2 100 % – minimal PEEP 5 cmH_2O – adequate tidal volume and respiratory frequency to obtain PaO_2/FiO_2 > 200 mmHg (> 26.7 kPa), $PaCO_2$ 35-45 mmHg (4.7-5.9 kPa).
– In cases where PaO_2/FiO_2 ratio < 200 mmHg (< 26.7 kPa), the procedure may cause cardiac arrhythmias/bradycardia/cardiac arrest and should be considered with caution, performed with alternative method, or abandoned (reasons recorded in the BD sheet).
– Disconnect the patient from the ventilator for a period of usually 3-5 mins (maximum 10 mins) – SaO_2 monitoring is mandatory to detect any drop, while administering O_2 through the endotracheal tube with a flow of 6-8 L/min.
– Attention to the diameter of the suction catheter and the risk of airway obstruction.
– Recruitment manoeuvre to be applied after reconnection in order to limit lung atelectasis.

'Possible alternative' procedures for apnoea test (if legally accepted in your country)

– After pre-oxygenation:
– Disconnect patient from the ventilator and connect to self-inflating bag with CPAP valve, supplied with an O_2 flow of 6 L/min connected to endotracheal tube, or
– Ventilator set up on CPAP mode without disconnection, or
– Hypoventilation with FiO_2 of 1.0 to obtain required $PaCO_2$ level, then CPAP for 1 min. with or without ventilator disconnection.

Collect sample of arterial blood after an interval of about 5 mins and reconnect the ventilator, if required $PaCO_2$ is achieved; if not, continue the test.
The test is positive if the $PaCO_2$ level increases by more than 20 mmHg (2.7 kPa) compared to the reference baseline value.
Some countries require a $PaCO_2$ level ≥ 60 mmHg (≥ 8.0 kPa).

Note: CPAP: continuous positive airway pressure. PEEP: positive end-expiratory pressure. Sources: [19-24].

nation of death by neurologic criteria; indeed, while brain function refers to a macrophenomenon that can be assessed at the bedside, brain activity refers to neuronal (not necessarily integrated) functions. In the context of death determination, 'permanent' refers to "loss of function that cannot resume spontaneously and will not be restored through intervention". On the other hand, the term 'irreversibility' refers to a situation that cannot return or resume. They also list the synonyms of 'brain death': 'brain circulatory arrest', 'cerebral arrest', 'cerebral circulatory arrest', 'cerebral death', 'coma *depassé*', 'irreversible coma', 'neurologic death', 'death by neurologic criteria', 'death of the brain', 'neurological determination of death' and 'death by brain criteria'.

A debate exits about the 'physiopathology' of BD as the death of every single cerebral neuron or loss of every brain-driven reflex [17]. In fact, a preserved neurohormonal function of the brain is manifested by the absence of central diabetes insipidus in around 50 % of DBD donors [18]. The authors stated that "It is recommended that BD/DNC be defined as the complete and permanent loss of brain function as defined by an unresponsive coma with loss of capacity for consciousness, brainstem reflexes, and the ability to breathe independently" [16]. Arguably, BD necessitates the irreversible cessation of the brain's superordinate control and its integrative capacities. Careful analyses of reported cases have never revealed a regaining of consciousness or survival after BD has been verified correctly, in accordance with professional guidelines.

Standardisation of the criteria for BD determination throughout the world would require changes in practice, recommendations and even laws of many countries. Changing methods and procedures that have been in place for many years, and which now allow organ transplantation with the support of health professionals and the population, may create disquiet if the changes are interpreted as evidence of an unsafe system currently being in use.

3.4. Clinical diagnosis of brain death

BD diagnosis first relies on a clinical examination and the study of brainstem function. It is the most immediate, reliable and easy way to determine BD in non-reactive comatose patients with devastating brain injuries, where no brain function is or will be possible, invariably ending in somatic death. Key aspects of the clinical diagnosis of BD are summarised in Table 3.1.

3.4.1. Preconditions for clinical examination

3.4.1.1. *Brain-death diagnosis: two mandatory criteria*

BD diagnosis should follow a strict step-by-step pathway, beginning with two absolutely mandatory criteria [25, 26]:

a. A structural cause and pathogenesis of BD must be identified.
Comas of unknown origin are not suitable for BD diagnosis. Catastrophic brain damage, when demonstrated, supports the conclusion of irreversibility of such condition (e.g. massive brainstem haemorrhage). The cause of coma is usually demonstrated by neuro-imaging but, in some cases, ancillary tests – such as laboratory tests or clinical findings (e.g. meningitis, encephalitis or poisoning, and early period after cardiorespiratory arrest) – may be necessary.
BD may be partially simulated by neurological clinical situations, such as locked-in syndrome, post-anoxic encephalopathy, minimally conscious states or persistent vegetative states. In such cases, any sign of consciousness or spontaneous brain-related movements including convulsions, any brainstem reactivity to stimuli or the presence of spontaneous breathing are key indicators for excluding BD. Rare cases of Guillain–Barré syndrome involving all peripheral and cranial nerves, endocrine crisis, snake bite or baclofen overdose (potentially reversible situations) can all mimic BD, leading to a potentially dangerous diagnostic error if the clinical evolution is not deeply investigated or proper ancillary tests are not performed.

b. Any factor that can interfere with the clinical diagnosis and make it unreliable must be excluded.

c. The absence of any confounding factors that can lead to a misdiagnosis is essential to the conclusion that the absence of brain function detected in the clinical examination is completely related to the structural cause identified above and irreversible.

d. The World Brain Death Project communication suggests that, prior to making a determination of BD, there should be neuroimaging evidence of intracranial hypertension or intracranial pressure measurements that equal or exceed mean arterial pressure (MAP) [16].

3.4.1.2. *Brain-death diagnosis: factors to exclude*

Severe physiological derangements must be excluded before performing the clinical examination to

ensure the reliability of BD diagnosis, which is the irreversible loss of cerebral functions [27]:

a. Core temperature should be > 35 °C: brainstem reflexes may disappear when core temperature drops below 28 °C. Moreover, the response to light is lost at core temperatures between 28 °C and 32 °C. Long-term hypothermia, particularly in anoxic brain injury, and therapeutic hypothermia (32 °C to 34 °C) both need a 24 h evaluation period (see §3.5.4.4).

b. Haemodynamic stability, adequate oxygenation and euvolaemia must be ensured: mean arterial blood pressure > 60 mmHg in adults (see Chapter 14 for paediatric concern).

c. Exclusion of metabolic conditions that may confound the clinical assessment (severe electrolyte, acid-base or endocrine disturbance).

d. Any possible effect of CNS-depressant drugs and neuromuscular blocking agents should be strictly evaluated and excluded (barbiturates, benzodiazepines, tricyclic anti-depressants etc.) Screening tests may be helpful, but some toxic agents may not be detectable by routine assessments (e.g. cyanides, lithium and fentanyl). A reasonable approach for unknown or suspected drugs or toxins is to prolong the observation period for 48 h to determine whether a change in brainstem reflexes occurs; if no change is observed, a confirmatory test must be performed [25]. If the substance known to be present cannot be quantified, the observation period should be at least five times the clearance half-life of the substance – excluding interferences by other drugs or organ dysfunction, e.g. Acute Kidney Injury Network (AKIN) classification for kidneys > II [28], liver dysfunction with total bilirubin level > 3 fold (expert opinion). Clinical diagnosis is allowed if serum drug levels are below the therapeutic range and/or clinical evidence shows that the neurologic deficit is not explained by the existence of the drug. In some situations, drug antagonists can be used (see also §3.5.4.2).

e. Extreme caution should be used whenever patients are subject to therapeutic hypothermia or non-pulsatile continuous-flow mechanical circulatory support devices, since these situations modify drug clearance, e.g. of propofol and baclofen. An appropriate time for neurologic recovery should be allowed or confirmatory tests should be used to achieve certainty about the irreversibility of neurologic findings [29].

f. The clinical examination including apnoea test must be complete, rigorous and reliable: possible pitfalls may depend on facial, ocular or high cervical trauma and pre-existing pupillary abnormalities. These factors may impede the examination of all the brainstem reflexes. Sleep apnoea or severe pulmonary disease resulting in chronic retention of CO_2 should lead to a tailored apnoea test. In all these circumstances confirmatory tests are recommended [27].

3.4.1.3. *Brain-death diagnosis: irreversibility*

Irreversibility of brain function loss due to a known devastating cerebral lesion is the key factor for BD diagnosis. Irreversibility has three factors requiring clinical judgment:

a. The cerebral lesion must be sufficient and congruent to be directly linked to total brain destruction.

b. Treatable and reversible medical conditions known to depress brain function should be excluded. If any potential confounding factor cannot be reversed or excluded, BD diagnosis must be completed with proper confirmatory ancillary tests.

c. The absence of brain function should be confirmed during an observation period clinically tailored to the type of lesion, age or other relevant factors but, in most countries, guided by national guidelines or legal procedures.

Confirmatory ancillary tests, e.g. those demonstrating the absence of cerebral blood flow (CBF), should be applied whenever there is a reasonable doubt or if needed for good practice or if needed by local or national recommendations or by state law. These confirmatory tests, once performed, may shorten the observation period.

As the interpretation of a clinical examination is dependent on these two items – irreversibility of brain function and confirmatory ancillary tests – and evidence of irreversibility is required for the final conclusion of BD, diagnosis should be performed by physicians experienced in neurologic-critical situations.

3.4.2. Clinical examination

The confirmation of BD through clinical examination is established by neurologic testing of comatose patients in whom there are no spontaneous breathing movements and no brainstem reflexes where the neurologic testing fulfils the above-mentioned preconditions (see §3.4.1).

Neurologic tests should be performed when physiological conditions (haemodynamic, metabolic,

respiratory and non-hypothermic) are stabilised, making possible a response from any living neurons. Before carrying out diagnostic tests that may have a negative effect on the brain, it is advisable to run tests that do not have such an effect, thus preventing further damage if death is not confirmed. The apnoea test should be the last to be performed, when the necessary rise in partial carbon dioxide pressure ($PaCO_2$) increases intracranial pressure with the risk of brain damage [25, 26]. If any brainstem function reflex is positive, or if in any way there are reasonable doubts about the BD diagnosis, the apnoea test should not be performed. If breathing movements are detected, the apnoea test should be aborted, and controlled ventilation restarted.

It is recommended to ventilate the patient with FiO_2 1.0 and adjust the ventilator to obtain normocapnia for 15-30 minutes before beginning the clinical examination.

The head of the bed should be elevated to 30°. Previous inspection of tympanic membranes is recommended in all cases to exclude lesions or cerumen that could diminish sensitivity of the oculovestibular reflex. In case of a traumatic aetiology, the presence of blood clots has a similar effect and is frequently related to possible temporal bone fractures (which can be associated with absence of facial anatomic integrity and/or that of auditory/vestibular nerve responses) [25]. In these cases, caution should be taken when drawing conclusions about the results of absence of facial motility and/or absence of vestibular reflexes, as they may not be related to the absence of brainstem function. This kind of pitfall also applies to other cranial or somatic deranged structures (nerves), and caution in final interpretation should be taken.

All brainstem reflex tests (before the apnoea test) should be performed under controlled ventilation. An arterial blood gas sample obtained just before the beginning of the physical exam is recommended, to confirm respiratory status and orientate the duration of the apnoea test.

3.4.2.1. *Brainstem reflexes*

Deep coma (Glasgow Coma Score of 3) must be confirmed at the beginning: the patient must be unresponsive to verbal stimuli, although movements related to medullary reflexes may still be present. However, the physician should disregard decerebrate and decorticate posturing or seizures at inspection, since these are signs of encephalic activity that would exclude BD. The physical examination of brainstem reflexes is summarised in Table 3.1.

3.4.2.1.1. Photomotor reflex (afferent II cranial nerve, efferent III cranial nerve)

In the Collaborative Study Criteria (published by the US National Institutes of Health in 1980), dilated and fixed pupils were considered mandatory, because mid-position fixed pupils can be seen in cases of drug intoxication [27, 30]. Nowadays, careful history and drug screening obtained before any BD diagnosis allows mid-position fixed pupils to be judged consistent with BD in the presence of negative toxicology screening. Usually, pupils are 4-6 mm in diameter, but may vary to unilateral or bilateral dilation size (9 mm). They are always fixed on light stimulation. Also no blinking reflex is noted upon stimulation.

3.4.2.1.2. Corneal reflexes (afferent V cranial nerve, efferent VII cranial nerve)

In BD, no blinking, tearing or reddening can be obtained upon corneal stimulation. The stimulus is obtained with physical contact of the edge of a swab over the limbal margins of the corneas; middle (central) corneal area stimulations should be avoided, as they are related to central vision where potential harm may occur with no evidence of superior threshold stimulus at that zone. To avoid this potential problem, stimulation with a drop of saline is recommended.

3.4.2.1.3. Oculovestibular and oculocephalic reflexes (afferent VIII cranial nerve, efferent III and VI cranial nerves)

In oculovestibular reflexes testing, the stimulus is an irrigation with 50 cc icy saline slowly into one external auditory canal with both eyes open; after instillation, waiting for at least 1 minute, any deviation of eye's axis or eye's movement and autonomic response must be excluded to fulfil BD criteria. Stimulation of the opposite auditory canal should be performed after a 5-min delay.

Alternatively, the oculocephalic reflexes may be tested: eyelids are kept open while the head is turned abruptly from side to side; observation of the eyes' position in the immediate seconds will reveal no change in the axis in brain-dead patients. In normal responses, the eye's axis follows the head movement with some delay.

Assessment of one or both reflexes depends on the physician's judgment, but oculovestibular tests are more popular, mainly in trauma cases, where sharp cervical movements may be dangerous.

Table 3.2. **Clinical observations compatible with a diagnosis of brain death [27]**

American Academy of Neurology protocol list of occasional phenomena that should not be misinterpreted as evidence for brainstem function:
• spontaneous movements of limbs other than pathologic flexion or extension response
• respiratory-like movements (shoulder elevation and adduction, back arching, intercostal expansion without significant tidal volumes)
• sweating, blushing and tachycardia
• hyperthermia
• normal blood pressure without pharmacologic support, or sudden increases in blood pressure
• absence of diabetes insipidus
• deep tendon reflexes, superficial abdominal reflexes or triple flexion response
• Babinski reflex.

3.4.2.1.4. Pharyngeal (nausea or gag) and cough reflexes (afferent IX cranial nerve, efferent X cranial nerve)

No response to posterior pharynx stimulation with a tongue blade and no response to tracheobronchial suctioning (carinal stimulation) must be observed, and no respiratory movements should occur at all.

3.4.2.1.5. Facial movement in response to noxious stimuli

No response to painful trigeminal (facial) area stimulation (i.e. temporo-mandibular joint zones or supraorbital nerves at the supraorbital ridges) must be observed. No reaction or grimacing must be observed after applying painful stimulus on body somatic areas (neck, thorax, limbs or abdomen) such as pressure on a nail bed.

It is always important to remember that any demonstration of arousal or awareness is not compatible with BD.

3.4.2.1.6. Atropine test (efferent X cranial nerve)

The atropine test consists of the intravenous administration of 0.04 mg/kg atropine, which will increase heart rate by more than 10 % of the baseline rate in non-brain-dead patients. Heart rate increase is obtained by stimulus at the nucleus of the vagus nerve, in the lower medulla. In brain-dead patients there is a lack of heart rate response. This test is easy to perform and important to confirm the neurological diagnosis of BD, stimulating by a pharmacological stimulus the same critical deep area of the brainstem investigated by the apnoea test. In most countries this test is not required by national guidelines. When indicated, it may be used as a complementary test before the apnoea test is performed.

3.4.2.1.7. Apnoea testing

The apnoea test aims at demonstrating loss of respiratory brainstem function. However, this test is at high risk of causing hypotension, hypoxia and cardiac arrhythmias if adequate oxygenation and volaemia are not achieved before testing. Sometimes, these complications create barriers for completing the test, leading to the need for additional confirmatory studies.

Prior to this test, the patient is pre-oxygenated with FiO_2 of 1.0 for at least 5 mins and a baseline arterial blood gas sample is obtained (objective pH 7.38-7.40; $PaCO_2$ 35-45 mmHg, i.e. 4.67-5.9 kPa). The patient is disconnected from the ventilator (while oxygenation is ensured by apnoeic oxygenation–diffusion with 6-8 L/min of O_2 through the tracheal tube), or maintained under continuous positive airway pressure mode (CPAP) and 100 % oxygen without any artificial drive support, to maximally stimulate the brainstem respiratory neurons (around 5-10 mins). An insufflation catheter with an outer diameter < 70 % of the endotracheal tube inner diameter may prevent inappropriate lung pressure and volume during the apnoea test [19]. Any ventilator movement or any ventilator drive are excluded by careful observation of the chest and/or meticulous capnographic monitoring. At the end of the test, a second arterial blood gas sample is obtained: if there is an increase of the $PaCO_2$ of more than 20 mmHg (2.7 kPa) compared to the reference sample, the test is indicative of cessation of respiration in absence of any ventilatory activity observed. In most countries, it is recommended that terminal $PaCO_2$ should be higher than 60 mmHg (≥ 8.0 kPa). Some countries also require a pH less than 7.40.

In the World Death Project, it is suggested that the targets should be pH < 7.30 and $PaCO_2$ > 60 mmHg (8.0 kPa) unless a patient has pre-existing hypercapnia, in which case it should be > 20 mmHg (2.7 kPa) above their baseline $PaCO_2$, if known [16].

Once an apnoea test is performed in a potential lung donor, lung collapse, atelectasis and oedema should be avoided. Recruitment manoeuvres performed after the apnoea test may improve the PaO_2/FiO_2 ratio and prevent acute lung complications [20].

In the case of serious lung damage with $PaCO_2/FiO_2$ ratio < 200, very fast desaturation followed by circulatory disturbances may be observed after ventilator disconnection. To avoid this, alternative methods of apnoea test based on the use of CPAP systems with oxygen supplementation may be recommended. First, as mentioned above, without ventilator disconnection under CPAP mode and trigger exclusion (ventilator self-cycling can be confused

with brainstem-mediated respiratory effort as a phenomenon of auto-triggering) [21]. This option is rarely possible nowadays, because for safety reasons the majority of modern ventilators have non-suspendable automatic apnoea backup ventilation. Alternatively, CPAP may be applied with self-inflating bag with CPAP valve supplied with an O_2 flow of 6 L/min connected to endotracheal tube [22] or with circle system of anaesthesia machine [23, 31, 32]. Another option for apnoea tests in extremely hypoxaemic patients is hypoventilation, with minute ventilation reduced approximately by 50 % (following pre-oxygenation), to obtain required $PaCO_2$ level. Afterwards, ventilation mode is switched to CPAP mode for 1 min with or without ventilator disconnection. Periodic arterial blood gas analysis should be taken until $PaCO_2$ achieves the required level [24].

3.4.2.2. *Spinal reflexes*

Since BD means loss of the encephalic function, neurologic activity depending on spinal cord may persist and be detectable, either clinically or in ancillary tests. In BD, complex withdrawal movements originating in the spine are possible, and must be differentiated from seizures, decortication and decerebration posturing movements, which indicate brainstem activity (and cortical activity in the case of seizures).

Several manifestations occasionally seen in BD patients should not be misinterpreted as evidence for brainstem function [27]. These manifestations (see Table 3.2) include not only spinal reflexes.

Respiratory acidosis, hypoxia or quick neck flexion may generate spinal cord responses. Spontaneous movements of the limbs with spinal mechanism of generation can occur and are more frequent in young adults. These spinal reflexes include flexion of the arms or fingers, slowly rising of the limbs or one limb off bed, gasping movements, spontaneous jerking of one leg and walking-like movement (so-called Lazarus signs). Multifocal vigorous myoclonus in the shoulders is occasionally seen in young patients. Respiratory-like movements are characterised by shoulder elevation and adduction expansion without any significant tidal volume being seen.

Other, much less common responses are sweating, blushing, tachycardia and sudden increase in blood pressure. These haemodynamic responses can sometimes be induced by neck flexion. Muscle stretch reflexes, superficial abdominal reflexes and Babinski sign are of spinal origin and thus do not invalidate the diagnosis BD. Patients may have initial plantar flexion of the great toe followed by sequential brief plantar flexion of the second, third, fourth and fifth toes after snapping of one of the toes ('undulating toe flexion sign').

Several studies confirm this phenomenon with a prevalence of about 50 % in cases of confirmed BD, and its presence does not alter but indeed confirms the reliability of BD diagnosis. In fact, recovery of spinal activity of the well-perfused and oxygenated spinal neurons occurs in hours or days after the immediate spinal shock, due to the ultimate brain-dying process leading to BD. Without any superior (encephalic) control, the spinal neurons easily react to even minimal stimuli (i.e. body touching, respiratory acidosis during the apnoea test, any painful stimulation and surgical stimuli during organ recovery) creating gross and never finalised body movements and huge vegetative response.

In one prospective study of cases with the diagnosis of BD confirmed by angiography, deep tendon and stretch reflexes were shown to be frequently absent in the first day of injury and to return after 24 h [33]. It was also noticed that brain-dead patients without spinal reflexes were also continuously haemodynamically unstable. Ipsilateral extension–pronation responses on upper chest pain stimulation were present in 33 % of cases and ipsilateral flexion withdrawal responses on L3/4 dermatome stimulation in 79 %. Wijdicks observed that spinal movements appeared during the apnoea test, on transportation of the patient, at the time of abdominal incision, or synchronously with the ventilator's activity and described them as occasions where 'slow body movements may even include a brief attempt of the body to flex at the waist, making it seem to rise' [25]. Consistent clinical documentation of BD and confirmation by an ancillary test will give the final evidence for BD (e.g. isoelectric EEG during movements).

3.4.2.3. *Clinical observations compatible with the diagnosis of brain death*

Next to spinal reflexes, some other phenomena can persist or appear but remain compatible with the diagnosis of BD. For example, the consequence of the persistence of certain hormonal activity dependent on the hypothalamic-pituitary axis can be seen (e.g., sweating, blushing and tachycardia; hyperthermia, normal blood pressure without pharmacologic support, absence of diabetes insipidus) [18].

Despite a cerebral circulatory arrest diagnosis in BD, trace blood flow responsible for maintaining hormone secretion by the hypothalamic-pituitary axis could exist. For example, the incidence of neurogenic diabetes insipidus secondary to the absence of antidiuretic hormone secretion in brain-dead patients has been reported in 46 % to 78 % of cases [34],

while several studies have shown that some patients maintain adequate levels of hypothalamic hormones [18]. These findings, together with the complex and variable hypothalamic vascularisation, could explain also the function of the thermoregulatory centre and thus hyperthermia in patients showing infection and BD [35].

In some situations, a ventilator autotriggering (VAT) can happen. This phenomenon can be described as a ventilator being triggered in the absence of patient effort, intrinsic respiratory drive or inspiratory muscle activity. It can mimic spontaneous ventilation creating a delay in the recognition of BD [36]. It can be due to cardiac oscillation, leak in the circuit, condensation, noise or artefact [37]. These studies emphasise that the apnoea test can only be assessed reliably when the patient is disconnected from the ventilator.

3.4.3. Observation period

Since the initial Harvard Committee report of 1968, all protocols mention the need for an observation period and repeated clinical examinations to confirm the initial diagnosis of BD. There is controversy about the irreversibility of the clinically observed status. However, particularly when an ancillary confirmatory test is used and the clinical evolution and the aetiology are well known, it may be clinically reasonable to confirm BD even when there is a short interval between two clinical examinations that include the apnoea test. In most countries, this clinical option is overcome by guidelines or rules that make it mandatory to legally declare death by neurological criteria.

Nevertheless, from the medical point of view, it may be better to confirm BD diagnosis over a period of time, mainly if the irreversibility of the damage responsible for brainstem function loss is not obvious, particularly in post-anoxic patients. As a diffusely accepted clinical rule due to the peculiar pathogenesis of a cerebral ischaemic-anoxic lesion, at least 24 hours should be the interval between the cerebral anoxic insult and a reliable clinical diagnosis of BD. In comatose survivor patients after cardiac arrest treated with therapeutic hypothermia, this interval should be extended up to 72 hours [38].

3.4.4. Brain-death declaration

BD is based on clinical criteria fulfilled by neurological examination, in some cases confirmed by ancillary test proving absence of metabolic/electrical cortical/encephalic activity or absence of CBF. Nevertheless, most countries define procedures that are mandatory to give legal and social validity to the clinical diagnosis. It is important to emphasise the need for all countries to have a protocol at national level for BD diagnosis. Having a national protocol has many benefits, including promoting safe practices and assuring that there are no diagnostic errors in the determination of death, protecting patients and healthcare professionals, improving public and professional confidence in the deceased donation process, and increasing the availability of organs obtained by ethically legitimate donation and procurement practices.

Practice varies widely, even among European countries, particularly in the number and professional background of physicians needed to perform from one to four clinical examinations, the observational period (which may last up to 72 hours, particularly in children, and may be reduced if ancillary tests are performed) and the mandatory or optional use of different ancillary tests [39, 40]. However, at least a preliminary ancillary test is recommended in all protocols either to overcome any residual doubt about the reliability of clinical observations, due to possible confounding factors, or to reduce the observation period.

Ultimately, harmonisation of European procedures remains one of the most important issues to improve the medical and social acceptance of the declaration of BD.

3.5. Ancillary tests for the diagnosis of brain death

Whatever the adopted concept is, 'brainstem death' or 'whole-brain death', the first step remains the clinical assessment of BD. Neurologic examination should be clearly consistent with a clinical BD state on the basis of a strict validation of all the required criteria (see §3.4.1 and §3.4.2) before performing any complementary test. The choice of ancillary study is a function of factors such as local facilities, equipment availability or special circumstances, e.g. children, non-airtight-cranium patients, residual circulation of sedative agents. Nonetheless, some national guidelines correctly state that ancillary tests that confirm irreversible cerebral circulatory arrest can be used as an appropriate tool for the decision on when neurologic examination can be done for the clinical assessment of BD (independently of leftover interaction caused by sedative drugs etc.). In the case of sedative drugs, the results of the particular ancillary test may be used too.

3.5.1. Brain blood-flow tests

3.5.1.1. *Digital subtraction angiography*

The classic four-vessel arteriogram has been for a long time the gold standard of CBF investigation in brain-dead patients since neither hypothermia nor CNS depressants interfere with it. Although an invasive method, digital subtraction angiography remains one of the recommended tests to be performed in Canada and the United States for the diagnosis of cerebral circulatory arrest [27, 41]. The cessation of circulation is not instantaneous, but progressive. Various gradual patterns, from partial or delayed intracranial arterial filling to no filling, all consistent with BD, can be observed:

a. Extreme slowing of arterio-venous circulation time (lengthening greater than 15 seconds is not compatible with cerebral function);
b. Cessation of cerebral arterial circulation in the Circle of Willis;
c. Total arrest of arterial contrast and lack of venous filling; the contrast material disappears retrogradely.

However, angiography has some disadvantages, such as the need to move the patient outside the ICU, the use of potentially nephrotoxic contrast agents and arterial puncture. Intravenous digital subtraction angiography is successfully used to verify cerebral circulatory arrest and based on the same principles as conventional arteriography.

3.5.1.2. *Angio-scintigraphy*

Following the development of lipophilic radio-substances, radionuclide CBF testing has interesting possibilities in BD diagnosis. Since the first era of ^{99m}Tc pertechnetate scintigraphy, angio-scintigraphy using ^{99m}Tc-labelled hexamethylpropyleneaminoxime (HMPAO) as a diffusible radiotracer has become a common test, performed in a large number of countries.

Angio-scintigraphy with ^{99m}TcHMPAO consists of two phases: the first, to evaluate the CBF, and the second, 5-10 mins after injection, in which static images in anterior, lateral right and lateral left projections are obtained, to evaluate the parenchymal capture. The lack of isotope uptake in brain parenchyma ('hollow skull phenomenon') confirms CBF cessation. Angio-scintigraphy with ^{99m}TcHMPAO is easy to carry out, highly sensitive and specific, with no interference from the patient's clinical conditions or the administration of CNS-depressant drugs. Like other CBF tests, scintigraphy does not show 100 % accuracy for BD diagnosis.

With or without radionuclide angiography, planar imaging continues to be the pillar for the scintigraphic confirmation of BD. Static planar imaging, with the use of ^{99m}TcHMPAO and multi-projection, can be used to evaluate the flow of supratentorial (cerebral hemispheres, basal ganglia, thalamus) and infratentorial structures (cerebellum, brainstem). Single-photon emission computed tomography gives cross-sectional information, but the reliability of the test to exclude flow and metabolism remains to be validated. Bi-planar imaging should be performed as a minimum.

Some authors show a sensitivity of 98.5 % for BD confirmation when using planar imaging without the use of specific brain tracers [42]. Other studies support the idea that the sensitivity of ^{99m}TcHMPAO planar imaging is very high while the specificity (absence of cerebral perfusion with clinical BD confirmation) is near 100 % [43].

This test does not require the use of iodinated contrast, is easy to interpret and exhibits high concordance with cerebral angiography. As a significant advantage, this CBF test is not influenced by CNS depressants, hypothermia or metabolic disorders. Its main limitation is that it might demonstrate CBF in patients with some degree of skull opening, such as children under 1 year of age, individuals with open head injuries or after extensive craniotomy [43].

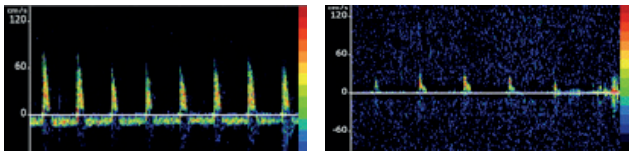
3.5.1.3. *Transcranial Doppler*

Transcranial Doppler (TCD) is a technique based on the ultrasonographic measuring of the blood velocity in arteries at the base of the skull. Besides its routine use for the management of patients with cerebrovascular and traumatic brain injuries, TCD is very useful in the diagnosis of the progressive circulatory cessation at the large intracranial arteries found in BD.

Brain circulatory cessation is, in most cases, due to an increase of intracranial pressure: when the level of intracranial pressure reaches the same value as the mean arterial pressure, the cerebral perfusion pressure approaches zero (cerebral perfusion pressure = mean arterial pressure – intracranial pressure). TCD can verify the kinetics of the cerebral circulation loss as a process that begins (especially in supratentorial pathology with intracranial hypertension) with a progressive decrease of the diastolic velocity, continuing with a separation of the diastolic and systolic wave, an inversion of the diastolic flow wave (reverberant flow), a disappearance of the diastolic wave and finally, especially in patients with a greater than 24 h cerebral circulatory arrest, the impossibility of obtaining any sign of cerebral flow. In 1998, the Task Force Group on Brain Death of the

Neurosonology Research Group of the World Federation of Neurology produced a consensus document in which two different sonographic patterns compatible with a diagnosis of BD were considered: 1. a reverberant flow pattern; 2. a pattern of systolic spikes (see Figure 3.1) [44].

Figure 3.1. **Transcranial Doppler wave forms of the middle cerebral artery compatible with brain death**



a. Reverberating flow b. Systolic spikes

Neurosonological Lab dataset, Dept. of Neurology, Medical University of Lublin, Poland, examinations performed by J. Wojczal MD PhD, certified neurosonologist.

The existence of inter-hemispheric or inter-compartmental (supratentorial/infratentorial) asynchronies on CBF can be also detected by TCD before completing the cerebral circulatory arrest.

In order to make a diagnosis of BD by TCD, the cerebral circulatory arrest must be documented by bilateral registration of reverberant diastolic flow and/or systolic spikes, in the anterior and posterior circulation, and in two different explorations separated by 30 mins. These findings must be demonstrated by insonation of both middle cerebral arteries (anterior circulation) and basilar arteries (posterior circulation) [45]. Additionally, some authors recommend also examination of internal carotid and vertebral arteries [45].

The accuracy of TCD for the diagnosis of BD varies in the literature. In a systematic review of the literature and meta-analysis, including 22 studies comprising 1 671 total patients, TCD sensitivity was 90 % (95 % CI, 0.87-0.92) and specificity 98 % (95 % CI, 0.96–0.99), suggesting that TCD is a highly accurate ancillary test for BD confirmation [46]. In some studies, the non-exclusion of patients without air-tight cranium (external ventricular derivation, large craniotomies) probably contributes to a lower TCD accuracy: these patients are not suitable for TCD investigation [47]. TCD can also be difficult in the absence of insonation for middle cerebral arteries using a transtemporal window; one solution could be the use of the orbital window for the insonation of the carotid siphon [48].

TCD is a non-invasive and easy-access technique at the bedside, and it can be repeated. It has also the advantage of not being influenced by the effects of CNS-depressant agents and does not require the use of a contrast medium. Although it has a high positive predictive value, not all countries recognise it as a legal test. This test needs a good level of expertise, and is operator-dependent. On the other hand, this is the perfect tool to detect the optimal time to perform a CBF study or EEG. A reproducible measurement of results by TCD, compatible with cerebral circulatory arrest in a time period of more than 30 mins, can be used as a confirmatory test. It is self-evident that, at a low blood pressure (MAP < 60 mmHg), the probability of obtaining signals as reverberating flow or systolic spikes decreases.

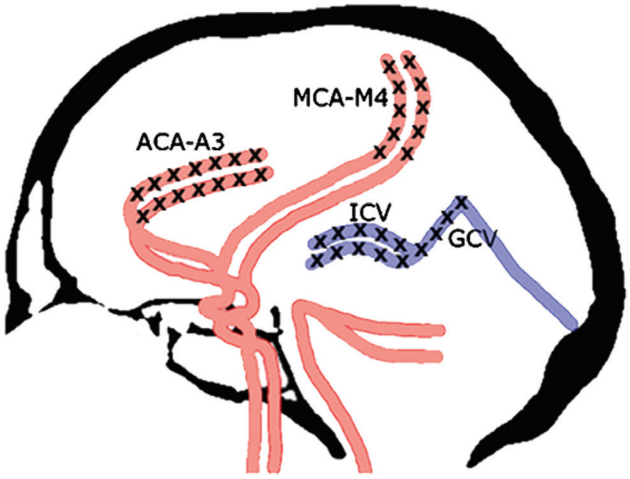
3.5.1.4. *Computed tomographic angiography*

In 1998, Dupas *et al.* described how computed tomographic angiography (CTA) could be useful in demonstrating a lack of intracerebral blood flow and reported the first application of CTA to the diagnosis of BD [49]. The authors proposed a 7-point CTA score for the confirmation of BD, according to opacification or non-opacification of the pericallosal arteries, cortical segments of the middle cerebral arteries, the internal cerebral veins and the great cerebral vein (see Figure 3.2a) [50]. In 2009, Frampas *et al.* introduced an alternative 4-point score based on the lack of opacification of cortical segments of the middle cerebral arteries and the internal cerebral veins (see Figure 3.2b) [51]. Since then, several major studies of this application have been published, and national guidelines have been introduced in several European countries (e.g., Austria, France, Germany, Italy, the Netherlands, Poland and Switzerland) [52-54]. Unfortunately, these guidelines are not standardised between countries and there are significant protocol differences in evaluation scales and scanning time. These variations may lead to discrepant diagnoses of cerebral circulatory arrest, especially in cases with borderline progression of cerebral oedema. Therefore, European unification of CTA protocols in BD diagnosis is warranted.

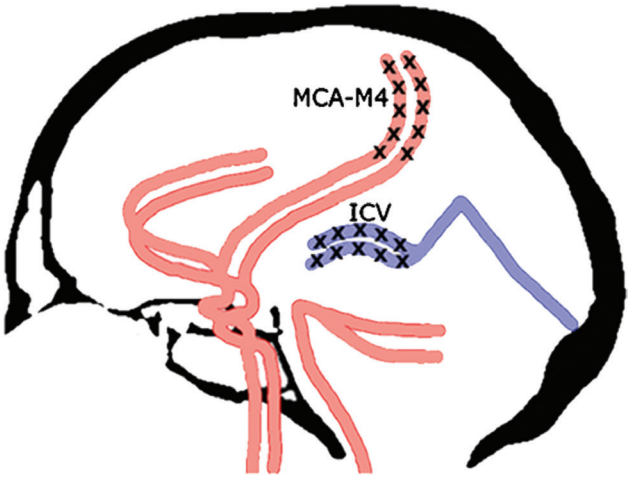
Two meta-analyses, including 10 studies published between 1998 and 2013, that compared the results of CTA in patients with BD diagnosis, reported its relatively low overall sensitivity of 85 % [55, 56]. However, these meta-analyses included older studies, whereas a more recent large multicentre trial with 82 brain-dead patients shows sensitivity > 96 % according to a 4-point score [54]. This difference could be explained by continuing technical progress in CT scanners, which allows assessment of faint opacification of cerebral vessels more precisely, together with the increasing experience of radiologists performing the test. Therefore, CTA should be considered as a valuable ancillary test in BD diagnosis.

Figure 3.2. **Criteria for the diagnosis of brain death by CTA**

a. Using a 7-point score



b. Using a 4-point score



(a) In the 7-point scale brain death is confirmed by a lack of opacification of the bilateral pericallosal artery (ACA-A3), the bilateral cortical segments of the middle cerebral artery (MCA-M4), the bilateral internal cerebral vein (ICV) and the great cerebral vein (GCV).
(b) In the 4-point scale brain death is confirmed when the bilateral MCA-M4 and the bilateral ICV are not opacified.
Adapted from: Sawicki, Bohatyrewicz, Safranow *et al. Neuroradiology* 2014;56:609 [50].

False negative CTA results (opacification still present in clinically confirmed BD) may be seen in rare situations like decompressive craniectomies, skull fractures, ventricular shunts, newborns and infants with pliable skulls. In such cases, other tests than CBF studies should be used to confirm BD. It should be mentioned that increase of intracranial pressure leading to BD is a continuous process and, secondary to it, cessation of cerebral circulation is continuous too. Therefore, at early stages after the onset of brain stem areflexia, brain oedema may not increase intracranial pressure above the blood pressure. In such situations an opacification of peripheral segments of cerebral arteries may still persist. Therefore, there should be a recommendation to perform CTA with a delay of > 6 h after the appearance of clinical signs of BD. If the first CTA test is negative, either the test should be repeated after 12 h or alternative pathways should be used for confirmation of BD/DNC according to national recommendations or laws.

CTA [56] has the advantages of being widely available, far less invasive and less technically complicated than the reference digital subtraction angiography (DSA), less time-consuming than cerebral scintigraphy and less operator-dependent than transcranial Doppler. When using a CTA test, physicians should also consider the possibility, at the same time, of completing the evaluation by a whole-body CTA scan (chest, abdomen and pelvis) giving a precise view of the entire vascularisation and organ morphology; it can also detect anatomical variants and contraindications to donation (see Chapter 6).

3.5.1.5. *Magnetic resonance angiography*

Magnetic resonance angiography could potentially be an alternative to CTA. Technical constraints, in particular the need to use MR-compatible devices (like ventilator and infusion pumps), along with limited experience and lack of proven superiority, often limit its use for the purpose of BD diagnosis.

3.5.1.6. *Computed tomographic perfusion*

Recent advances in CT technology allow whole brain perfusion testing which makes the method a promising alternative for application in BD diagnosis in the near future. Computed tomography perfusion (CTP) could be used as the first-choice method for assessing brain tissue perfusion in designated areas – ROIs (regions of interest), including the brain stem – with capability of simultaneous visualisation of cerebral vasculature in multiple time points as Timing-Invariant CTA. Such combined technique allows assessing vascular filling and parenchymal perfusion with single injection of 40-50 mL of contrast medium *v.* 80 mL used for CTA.

Perfusion assessment may also be a conclusive test in rare cases in which the contrast of cortical arteries or the internal cerebral veins is found and, according to currently used criteria of cerebral circulatory arrest, cannot be confirmed, which consequently delays BD diagnosis [57]. Based on a validating study including non-brain-dead controls, Poland legalised CTP as an ancillary test for the diagnosis of BD in the population over 12 years of age in January 2020. Initial experiences in clinical application of the

test are promising [58]. Whereas there is no universally recognised consensus on the technique and criteria for diagnosis of cerebral circulatory arrest with CTP, more comprehensive case-control studies are warranted [16].

3.5.2. Electrophysiologic tests

3.5.2.1. *Electroencephalography*

An electroencephalogram (EEG) is a conventional and valuable test for diagnosing BD using the evidence of electric cerebral (cortical layer) inactivity. Standard EEG measurements cover the electrical activity only of the cortex and not of the brain stem. Prerequisites such as core temperature above 35 °C and lack of sedative agents should be respected before testing. Otherwise, the results of the EEG recording cannot be validated.

The most accepted criteria when performing an EEG study for the diagnosis of BD were approved by the American Electroencephalographic Society [59], which specified that a minimum of eight electrodes must be placed on the scalp, as well as a reference electrode (to detect electric interference in the environment of the ICU), with inter-electrode distances of at least 10 cm, placed in frontal, temporal, occipital regions with impedances under 10 000 ohms, but over 100 ohms. The EEG record must be obtained over a period of at least 30 minutes; sensitivity must be increased from 7 μV/mm to at least 2 μV/mm, with inclusion of appropriate calibrations.

Table 3.3. **Advantages and disadvantages of ancillary tests for the diagnosis of brain death**

	Advantages	**Pitfalls and disadvantages**
Electroencephalography	Bedside Wide availability No requirement for contrast medium	Presence of artefacts Examination of supratentorial structures, but not infratentorial Influenced by depressants of CNS, hypothermia and hypotension
Multimodal evoked potentials	Bedside Allows monitoring Less influenced by depressants of CNS and hypothermia than electroencephalography	Examination of few structures of CNS
Transcranial Doppler	Bedside Non-invasive No need to use contrast medium Can be repeated frequently Can show cerebral circulatory arrest as a process Not influenced by depressants of CNS	False positive flow in cases of non-hermetic cranium (big fractures of skull, decompressive craniectomy, cerebrospinal fluid drains) Lack of sonic window in some patients Operator-dependent (high level of training) Appropriate blood pressure required
Angiography	Not influenced by depressants of CNS	Invasive Not available in all hospitals Use of potentially nephrotoxic contrast agents Need to move the patient out of ICU False positive flow in cases of non-hermetic cranium (serious fractures of skull, decompressive craniectomy, cerebrospinal fluid drains)
Angio-scintigraphy	Less invasive No use of iodinated contrast Not influenced by depressants of CNS	False positive flow in cases of non-hermetic cranium (serious fractures of skull, decompressive craniectomy, cerebrospinal fluid drains) If negative for BD, it cannot be repeated until elimination of radiotracer Need to move the patient out of ICU (except for portable gamma camera)
Computed tomographic angiography	Not influenced by depressants of CNS Operator-independent Fast, widely available, technically uncomplicated	False positive flow in cases of non-hermetic cranium (serious fractures of skull, decompressive craniectomy, cerebrospinal fluid drains) Need to move the patient out of ICU
Computed tomography perfusion	Not influenced by depressants of CNS Operator-independent High sensitivity	Need scanner able to perform whole brain perfusion and dedicated software Need radiologist with expertise in analysing CTP Not widely legalised (Poland only) Need to move the patient out of ICU

In order to avoid attenuation of low-voltage fast or slow activity, whenever possible, high-frequency filters should not be set below a high-frequency setting of 30 Hz, and low-frequency filters should not be set above a low-frequency setting of 1 Hz. The high levels of sensitivity set on the electroencephalography machine increase the number of artefacts, which are plentiful in an ICU because of the presence of multiple devices.

In brain-dead patients, there should be no EEG reactivity to intense somatosensory, auditory or visual stimuli. A simultaneous electrocardiographic record should be made to detect electrical activity due to the cardiac activity (spike of QRS complex), co-existing with the EEG record. In the case of electro-myographic artefacts interfering during the record, these must be eliminated through the use of a neuromuscular blocking agent. Under these strict conditions of electro-cerebral inactivity or electro-cerebral silence (or other synonyms such as flat EEG), BD can be diagnosed if no electrical activity of the brain is recorded. If any doubt persists about the electro-cerebral inactivity, another EEG should be performed after an interval of usually 6 h. In some countries, two EEGs are mandatory as a legal requirement for the confirmation of BD.

The advantages of an EEG are performance at the bedside, no requirement for contrast medium and wide availability. Its main disadvantage is that it might demonstrate an absence of electrical activity in the presence of confounding factors, namely, severe metabolic disorders, hypothermia and CNS depressant effects. In this case, CBF imaging must be performed [25].

In the World Death Project, "it is suggested that EEG no longer be used routinely as an ancillary test in adults" except if mandated by laws or if in conjunction with evoked potentials and interpreted using legal criteria or recommendations [16]. Nevertheless, in certain situations (difficulty of access to certain examinations, difficulties in transport etc.), this tool can remain useful, after a well-conducted clinical examination.

Nevertheless, the existence of a flat EEG must not be considered as a synonym of BD but must always be accompanied by a complete clinical examination to confirm BD [60].

3.5.2.2. *Multimodal evoked potentials*

The multimodal evoked responses to luminous, sound and electrical stimuli examine the visual, auditory and somatosensory pathways at different levels. These give information regarding the integrity of the pathways or their exclusive functional extension to the peripheral nervous system. Among the different modalities of the evoked potentials, the auditory brainstem responses (ABRs) and somatosensory evoked potentials of short latency for median nerve stimulation (SEPs) have shown the best results in BD diagnosis [60]. In BD, evoked potentials are characterised by the disappearance of all waves corresponding to intracranial nerve generators and the persistence of activities of extracranial origin. In the auditory evoked potentials of the brainstem, all evoked responses of encephalic origin disappear, with only the presence of wave I, generated in the auditory nerve in the extracranial area. On the other hand, somatosensory evoked responses that demonstrate the spinal cord as the highest level of nerve-signal processing are compatible with BD (assuming that no isolated infratentorial devastating cerebral lesion exists).

One of the hypothetical advantages of evoked potential technique is its resistance to CNS-depressant drugs, such as barbiturates, and hypothermia. It is a non-invasive technique with a bedside approach that allows monitoring and follows the evolution of the patient. However, the accuracy of evoked potentials in the diagnosis of BD is still open to discussion, possibly due to lack of experience with the method except in specialised centres [60, 61].

3.5.3. Other tests

Other instrumental tests have been described as useful add-on tools for BD diagnosis, measuring cerebral electrical activity (e.g. bispectral index – BIS), intracranial and cerebral perfusion pressure, decrease in cerebral consumption of oxygen etc. However, their lack of accuracy makes them useless, since their role in BD diagnosis is not confirmed by appropriate studies.

3.5.4. Special circumstances

Ancillary tests, when used to confirm BD, require caution in special situations: patients with non-airtight cranium, patients under the effects of CNS-depressant drugs, and infants and children (for infants and children, see §3.6).

3.5.4.1. *Decompressive craniectomy, skull defects and ventricular drains*

The absence of a cranial-airtight skull induces changes in the normal balance of extracranial/intracranial pressure. As a consequence, tests exploring CBF show a decrease in diagnostic accuracy, particularly in the following causes of persistent CBF in brain-dead patients [51]:

- infants with pliable skulls;
- decompressing fractures;
- ventricular shunts;
- ineffective deep brain blood flow;
- reperfusion;
- extracranial herniation of intracranial vessels;
- jugular reflux;
- emissary veins; and
- artefacts of excessive pressure in contrast injection.

For example, in the case of skull defects (decompressive craniectomy, external drains, infants, etc.), because the increase of intracranial pressure may be partially compensated, the use of CBF tests for BD diagnosis may lead to false negative results. To avoid a delay in the diagnosis, the use of other tests such as EEG and multimodality evoked potentials (or angio-scintigraphy) is recommended, as well as correct use of pathways in examination in such circumstances as described in national recommendations and laws.

Table 3.4. **Half-life of some drugs**

	T1/2
Fentanyl	219 min
Alfentanyl	100 min
Remifentanyl	10 min
Naloxone	64 min
Midazolam	2-4 h
Diazepam	20-50 h
Flumazenil	0.7-1.3 h
Propofol	30-90 min
Pentobarbital	15-50 h

3.5.4.2. *Drugs depressant of central nervous system*

Excluding the impact of depressive drugs or toxins for the diagnosis of BD can be difficult for several reasons.

First, the patient may have taken medication or drugs before arriving at the hospital. A large screening test does not allow identification of all possible drugs. It is more important to know precisely what happened and in particular to know the causes of BD.

Second, because drug elimination can be impaired by organ dysfunction (e.g. kidney, liver), hypothermia (see §3.5.4.4) or hypotension, it is recommended to wait up to five half-lives of medications, check that administration dosage was appropriate and if available, measure drug plasma levels (rather than semi-quantitative detection). Drug plasma level must be below therapeutic levels. A huge amount of data can be found in the literature [62]. Table 3.4 shows the half-life of some drugs. Remember that this half-life can be prolonged by the time of infusion (context-sensitive half-lives) [63].

Third, the administration of high doses of barbiturates and other CNS-depressant drugs can interfere with the clinical examination. EEG is very sensitive to this confounding factor. Thiopental administered in continuous infusion, as a result of the wide range of plasma concentrations corresponding to efficacy (25-50 mg/L) and toxicity (30-70 mg/L), does not have a well-established therapeutic range because of the overlap between the two [64]. Long-term infusion increases thiopental levels, which remain elevated for more than six days in cerebrospinal fluid and serum after termination of its administration.

The value of serum levels of individual drugs is highly controversial; in many countries the use of ancillary tests (perfusion, electrophysiology) is mandatory in such cases. But, in daily practice, correlation between quantitative CNS drug dosage and depth of coma is weak. There is no unanimous opinion about how to make the diagnosis in these cases of CNS-depressant drugs, and there are different opinions on the best policy to apply: waiting until the plasmatic levels of barbiturates or other measurable depressant drugs decrease to infra-therapeutic levels (most reasonably), or waiting for the diagnosis until these levels reach zero. In some situations, the use of antagonists like flumazenil (in case of benzodiazepine administration) or naloxone (in case of opioids administration) can be helpful before performing a clinical exam or an EEG, but dosing and timing are not clearly defined. Inaccurate BD determination by clinical testing may occur. In a review of the literature from 1 January 1960 to 10 June 2015, ten case reports of BD mimicry were found (three baclofen, two snake bites and one each of valproic acid, amitriptyline, mixed diazepam + ethylene glycol, bupropion and phorate, an organic phosphorus compound) [9].

Furthermore, all clinical evidence explaining the observations may be more important than just relying on some measurements of blood levels that do not well explain the clinical situation. On the other hand, considering cases of isoelectric EEG due to the effect of drugs, the use of other techniques – such as techniques that examine CBF – could help to confirm the diagnosis, since they are not affected by CNS-depressant drugs.

3.5.4.3. *Patients with therapeutic extracorporeal membrane oxygenation (ECMO)*

Some patients, due to refractory respiratory failure or due to cardiogenic shock, can be treated

with extracorporeal membrane oxygenation (ECMO) (veno-venous or arterio-venous). Some of these patients may develop BD and become DBD donors. Despite severe medical conditions, some organs can be suitable for transplantation [65]. To diagnose BD in this situation, the preconditions are the same (no sedation etc.). The physical examination can also be done normally.

The biggest issue is performing the apnoea test. Some authors suggest adding CO_2 in the system to avoid hypoxaemia [66]. Bein *et al.* describe an algorithm for diagnosing BD in individuals on ECMO [67]. Basically, the test consists in gradual removal of ventilator, introducing CPAP with $FiO_2 = 1.0$, increase ECMO-FiO_2 to 1.0, and reduction of sweep gas flow to a value allowing achievement of target value of $PaCO_2$ and pH, avoiding desaturation at the same time. The targets to reach are the same (see §3.4.2.1.7) – e.g. $PaCO_2$ of at least 60 mmHg, pH < 7.30 – although it can take longer to reach these targets in a patient with ECMO support [16].

3.5.4.4. *Brain death diagnosis after treatment with targeted temperature management (TTM)*

After cardiac arrest, it is recommended to induce targeted temperature management. This treatment needs administration of sedatives and therefore can affect the way of performing BD diagnosis because it can alter pharmacokinetics and pharmacodynamics of sedatives given [68]. In this situation, it is recommended to wait 24 h after rewarming to ≥ 36 °C before performing a clinical examination and apnoea test. If the patient has received a sedative agent, the clinical examination must be delayed until at least 5 elimination half-lives of the drug and an ancillary brain blood-flow study should be performed [16].

3.5.4.5. *Confusing situations*

The clinician must be aware of three confusing situations.

First, despite a clinical diagnosis compatible with BD, there may be a presence of blood flow in an ancillary test. This discrepancy is due to differences in the sensitivity of the clinical examination and of blood flow determined with ancillary tests performed relatively soon after the neurological event. It can also be due to technical problems in assessing brainstem perfusion, and differences between blood flow and function as indicators of irreversible loss of brain function. It has been described with all the ancillary tests [69].

Second, the undocumented fear exists that the ancillary test may demonstrate absence of blood flow in vessels with significant impact on brain perfusion while we yet lack clinical signs of brain-stem failure. This may be explained either by the fact that the blood flow test has technical limitations that have not been considered properly or by the existence of anatomic vessel variants that have not been considered [70].

Third, the presence of infratentorial lesions can be source of a lot of confusion. In some countries, in cases of infratentorial lesions (e.g. devastating brain-stem bleeding) measurement of the functional failure or non-perfusion of supratentorial structures is required. In such cases, the brain-stem failure may precede the terminal failure of upper cortical lesions up to days before this event occurs due to secondary hydrocephalus after infratentorial herniation.

For these reasons, performing a complete physical exam in appropriate conditions is fundamental before using an ancillary test to confirm BD if needed.

In summary, no test shows 100 % accuracy covering all circumstances of BD. CBF studies are not influenced by confounders such as hypothermia or sedative agents, unlike EEG. In the case of non-airtight cranium, it is better to use an EEG to confirm the clinical diagnosis of BD. When available, four-vessel angiography, radionuclide CBF testing, TCD, CTA and EEG are currently the most widely used and recognised, with a legal value in confirming BD. Choosing one test over another requires a good knowledge of the advantages and limitations of each test and also of their technical requirements. They should be performed and documented by qualified and competent physicians. The final result of the confirmatory test should be documented in the medical report together with a checklist to ensure that each step of the BD diagnosis process has been validated beyond doubt. National recommendations and laws have to provide such checklists or protocols to be used locally.

3.6. Brain-death diagnosis in infants and children

BD diagnosis in a child is a rare event in any paediatric or neonatal ICU. As outlined in section 14.6, specific protocols must be used for BD diagnosis depending on the particular age and in accordance with national guidelines (see Appendix 4 and Chapter 14).

With respect to the development status and therefore different pathophysiology of the impact of devastating brain lesions in newborns, infants and toddlers versus adults, different sets of redundant investigation loops are in place: in general, they consist of a chain of clinical examination plus ancillary test,

followed by an observation period and a second confirmatory set of clinical examination plus ancillary test. Thereby the limitations of each ancillary test should be taken into account as well as the issue of premature newborns (in many countries defined by a cut-off around the 37th week of gestational age). Depending on the national guidelines, after an age of 1 to 3 years the rules for adults are applied [71]. All countries have different age limits, on which depend the formal limitations for ancillary tests (or the need to use them at all) as well as the need to call in a paediatric expert (see §14.6). Beyond the special issues outlined in §14.6, the principles of death determined by neurologic criteria in adults outlined in this chapter apply to paediatric donor candidates too.

It is highly recommended to refer to and adhere to the national laws and/or guidelines in place in order to avoid formal errors.

3.7. Implications of brain-death diagnosis

Once a BD declaration is made at the end of the observation period, an individual is pronounced legally dead. Certification of death is the final common result of the process of death determined by either cardio-circulatory or neurologic criteria. In most countries, mandatory procedures for certification are based on specific legal requirements, including continuous observation for a variable number of hours in the case of neurological criteria, or the documentation of cardiac arrest for 5-20 minutes in the case of circulatory criteria. This period is aimed at proving the irreversibility of detected signs and BD. In most countries, an independent committee of specialists who perform the tests and finally sign the certificate is required for BD declaration.

Death should be declared when it is confirmed by neurologic criteria, not at the time when the ventilator was removed or at the time of circulatory arrest. It should be made clear to professionals and relatives that, after a BD declaration, any legal or mourning procedures – including autopsy and funeral – can now be performed and last wills can be probated.

As death (e.g. irreversible total brain failure) is unique, but may be declared on the basis of two different mechanisms (e.g. following circulatory/respiratory arrest or after direct devastating cerebral injury), clear pathways should be defined, balancing uniform policies to be followed after the death declaration with appropriate concern for the feelings of the family as well as for any religious and social considerations.

Establishing a clear course of action after the BD declaration is of paramount importance and its implication cannot be influenced by the significant differences in procedures for death certification among European countries [39], particularly when BD is not followed by organ donation. In this case, physicians should act wisely and humanely, explaining the situation to the relatives, making it clear that withdrawal of mechanical ventilation will not make the patient die but that continued ventilation is unnecessary, and therefore inappropriate, for a patient already dead. The only reason to maintain ventilation for a predefined period of time (12-24 h) is to preserve the organs if consent is available for donation. ICU personnel should be properly educated and prepared to face the moment of ventilator withdrawal and waning cardiac function, explaining – to relatives and others concerned – the possible occurrence of spinal reflexes and the clinical, ethical and legal significance of their act. Appropriate answers should be given to respond to any doubts concerning BD coming from relatives and professionals, taking into consideration the personal and psychological concerns of critical-care personnel and clarifying roles and responsibilities in BD determination and *post mortem* procedures.

Nevertheless, some patients who fulfil BD criteria but present absolute contraindications or opposition to organ donation are not promptly disconnected from ventilation after BD declaration for several reasons; cardiac arrest will then occur within hours or days. Surprisingly, this confusing situation still occurs, because of either family opposition or physicians' attitudes that reflect doubts about BD as real death or because BD is not accepted for religious reasons [72]. In the case of donation refusal after BD confirmation, the legal opportunity to withdraw life-sustaining therapies – mainly ventilator support – is an absolute right which should be clearly stated in the legal framework surrounding BD declaration. Certain religious groups do not accept BD determination and some authorities have permitted an opt-out for faith groups that prevents clinicians from declaring BD in these patients. To varying degrees, this situation exists in Israel, the US (New Jersey, New York, California and Illinois) and Japan; however, no European country has a requirement to consult the family on how to terminate care. Consequently, it is important to raise the public's awareness of BD implications: the public needs to fully understand that the declaration of death cannot be the family's decision and that BD is completely equivalent to the irreversibility of the more traditional cardio-respiratory death.

At the same time, practitioners should be sen-

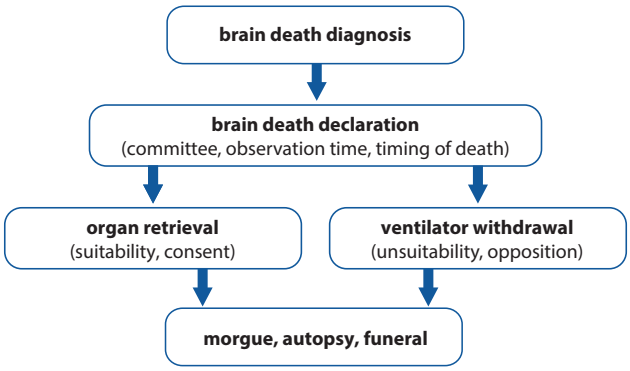
sitive to the feelings of families who suddenly have to face the death of their loved one. Thus, it seems reasonable to give the family some time to understand the process and absorb the concept of BD, and to support the relatives during the whole process of diagnosis, observation and declaration of death, by honest, empathic, clear and understandable information and explanations. Nevertheless, hospital policies and practices should be as uniform as possible [73].

BD in a pregnant woman is an exception: intensive support can be prolonged after BD for days and weeks, after ethical approval and family request, to allow adequate fetal maturity prior to delivery and organ donation, where appropriate [74]. In practice, as spinal cord function may recover after an initial 'shock' and primitive medullary reflexes can establish a level of circulatory integration and body metabolism, intensive care techniques can compensate in the dead person for the loss of brain function for months. This is accompanied by functions that are not strictly brain-dependent such as the immune response and the inflammatory responses, growth of the body and hair, wound healing and, finally, gestation of a fetus [75].

Only a few national laws (in seven European countries) indicate that death has to be determined by neurologic criteria regardless of potential organ donation, in all cases as soon as all the criteria of BD are completely fulfilled. In other countries, according to the law, death determination by neurologic criteria is not mandatory if donation is not expected. In reality, even if national laws always require declaration according to BD criteria, this procedure is rarely applied when either unsuitability or opposition is already known. In reality, the number of brain-dead patients may be significantly underestimated because of end-of-life choices leading to cardiac arrest after withdrawal of life-support therapy, personal judgment of medical unsuitability for organ donation or unfavourable attitudes of individual ICU physicians towards BD. In these cases, brain-stem reflexes or apnoea may not be tested or documented [76]. An audit of all deaths in British ICUs showed that brain-stem tests had not been performed in over 30 % of persons in a likely BD condition [77].

Public campaigns on organ donation could take advantage of public awareness of a clear and independent concept of death determination. National regulations and scientific guidelines should ideally include, in addition to a solid scientific basis for death determination, unambiguous procedures regarding all the possible implications of BD declaration and a clear indication about the time of death (see Figure 3.3). These recommendations could help in managing real situations in which the delicate relationship between medical practice and relatives, ethics and law may strongly affect the extent of social understanding of death declaration and organ donation possibility as normal parts of end-of-life care in an ICU [78].

Figure 3.3. **Management algorithm of brain death**



Social confidence in BD diagnosis and the bereaved family's trust in the dead donor rule would benefit from BD declaration being standard practice in all subjects who fulfil BD criteria. This medical practice could support the fundamental idea that all citizens must be equal in death: there is no difference between potential donors and other patients.

3.8. Conclusions

Making a diagnosis of brain death is an important part of the donation chain. It must be done by trained professionals, in a rigorous, systematic manner guided by the recommendations. Confounding circumstances must be eliminated. It should include a rigorous clinical examination and may involve confirmatory tests.

It is primarily a medical diagnosis. Legal requirements must be considered in a second step. A high-quality diagnosis enables the general population to have confidence in the diagnosis of death as well as allowing identification (to those with a right to know) of donors and the personnel taking care of them.

Research agenda

From the literature and discussion of the available evidence, several topics have been identified for which evidence is inconsistent, insufficient or non-existent. The authors of this guide recommend that future research, where possible in well-designed randomised clinical trials, should focus on the following research gaps:

1 What MAP should be recommended for a BD

diagnosis in adults (e.g. ≥ 65 or 60 mmHg)?
2 What core temperature should be recommended for a BD diagnosis (e.g. ≥ 34 °C, 35 °C or 36 °C)?
3 Need for harmonisation of computed tomographic perfusion (CTP) criteria.
4 Studies to confirm appropriate use of CTA in paediatric populations.
5 Monitoring of implementation of CTA/CTP in national guidelines, subsequently monitoring their sensitivity and specificity achieved by different scales in routine use.
6 Fundamental research explaining hyperthermia in persons with BD/DNC.

3.9. References

1. A definition of irreversible coma. Report of the Ad Hoc Committee of the Harvard Medical School to Examine the Definition of Brain Death. *JAMA* 1968;205:337-40. https://doi.org/10.1001/jama.205.6.337.
2. Machado C, Korein J, Ferrer Y *et al.* The Declaration of Sydney on human death. *J Med Ethics* 2007;33:699-703. https://doi.org/10.1136/jme.2007.020685.
3. Lassen HCA. A preliminary report on the 1952 epidemic of poliomyelitis in Copenhagen with special reference to the treatment of acute respiratory insufficiency. *Lancet* 1953;261:37-41. https://doi.org/10.1016/S0140-6736(53) 92530-6.
4. Wertheimer P, Jouvet M, Descotes J. À propos du diagnostic de la mort du système nerveux dans les comas avec arrêt respiratoire traités par respiration artificielle ['Diagnosis of death of the nervous system in comas with respiratory arrest treated by artificial respiration']. *Presse Med* 1959;67:87-8.
5. Mollaret P, Goulon M. Le coma dépassé ['The depassed coma' (preliminary memoir)]. *Rev Neurol (Paris)* 1959;101:3-15.
6. Diagnosis of brain death. Statement issued by the honorary secretary of the Conference of Medical Royal Colleges and their Faculties in the United Kingdom on 11 October 1976. *BMJ* 1976;2:1187-8. https://doi.org/10.1136/bmj.2.6045.1187.
7. European Directorate for the Quality of Medicines and Healthcare. *Guide to the Quality and Safety of Organs for Transplantation*. Strasbourg: Council of Europe 2018.
8. Wesslau C, Grosse K, Krüger R *et al.* How large is the organ donor potential in Germany? Results of an analysis of data collected on deceased with primary and secondary brain damage in intensive care unit from 2002 to 2005. *Transpl Int* 2007;20:147-55. https://doi.org/10.1111/j.1432-2277.2006.00413.x.
9. Neavyn MJ, Stolbach A, Greer DM *et al.* ACMT Position Statement: Determining brain death in adults after drug overdose. *J Med Toxicol* 2017;13:271-3. https://doi.org/10.1007/s13181-017-0606-8.
10. Kramer AH, Zygun DA, Doig CJ, Zuege DJ. Incidence of neurologic death among patients with brain injury: a cohort study in a Canadian health region. *CMAJ* 2013;185:E838-45. https://doi.org/10.1503/cmaj.130271.
11. Sprung CL, Ricou B, Hartog CS *et al.* Changes in end-of-life practices in European intensive care units from 1999 to 2016. *JAMA* 2019;322:1692. https://doi.org/10.1001/jama.2019.14608.
12. Domínguez-Gil B, Coll E, Elizalde J *et al.* Expanding the donor pool through intensive care to facilitate organ donation: results of a Spanish multicenter study. *Transplantation* 2017;101:e265-72. https://doi.org/10.1097/TP.0000000000001701.
13. WHO Regional Office for Europe, European Commission and the European Observatory on Health Systems and Policies. Covid-19 health system response monitor, available at www.covid19healthsystem.org/mainpage.aspx, accessed 18 July 2021.
14. Matesanz R, Coll E, Domínguez-Gil B *et al.* Benchmarking in the process of donation after brain death: a methodology to identify best performer hospitals. *Am J Transplant* 2012;12:2498-506. https://doi.org/10.1111/j.1600-6143.2012.04128.x.
15. Lewis A, Bakkar A, Kreiger-Benson E *et al.* Determination of death by neurologic criteria around the world. *Neurology* 2020;95:e299-309. https://doi.org/10.1212/WNL.0000000000009888.
16. Greer DM, Shemie SD, Lewis A *et al.* Determination of brain death/death by neurologic criteria: The World Brain Death Project. *JAMA* 2020;324(11):1078-97. https://doi.org/10.1001/jama.2020.11586.
17. Nair-Collins M, Miller FG. Current practice diagnosing brain death is not consistent with legal statutes requiring the absence of all brain function. *J Intensive Care Med* 2020:088506662093903. https://doi.org/10.1177/0885066620939037.
18. Nair-Collins M, Northrup J, Olcese J. Hypothalamic–Pituitary Function in Brain Death: A Review. *J Intensive Care Med* 2016;31:41–50. https://doi.org/10.1177/0885066614527410.
19. Henry NR, Marshall SG. Apnea testing: the effects of insufflation catheter size and flow on pressure and volume in a test lung. *Respir Care* 2014;59:406-10. https://doi.org/10.4187/respcare.02499.
20. Paries M, Boccheciampe N, Raux M *et al.* Benefit of a single recruitment maneuver after an apnea test for the diagnosis of brain death. *Crit Care* 2012;16:R116. https://doi.org/10.1186/cc11408.
21. Dodd-Sullivan R, Quirin J, Newhart J. Ventilator autotriggering: a caution in brain death diagnosis. *Prog Transplant* 2011;21:152-5. https://doi.org/10.7182/prtr.21.2.0685l073531lr120.
22. Hocker S, Whalen F, Wijdicks EFM. Apnea testing for brain death in severe acute respiratory distress

syndrome: a possible solution. *Neurocrit Care* 2014; 20:298-300. https://doi.org/10.1007/s12028-013-9932-0.

23. Shrestha GS, Shrestha PS, Acharya SP *et al.* Apnea testing with continuous positive airway pressure for the diagnosis of brain death in a patient with poor baseline oxygenation status. *Indian J Crit Care Med* 2014;18:331-3. https://doi.org/10.4103/0972-5229.132510.
24. Ahlawat A, Carandang R, Heard SO, Muehlschlegel S. The modified apnea test during brain death determination: an alternative in patients with hypoxia. *J Intensive Care Med* 2016;31:66-9. https://doi.org/10.1177/0885066615599086.
25. Wijdicks EF. The diagnosis of brain death. *N Engl J Med* 2001;344:1215-21. https://doi.org/10.1056/NEJM200104193441606.
26. Gardiner D, Shemie S, Manara A, Opdam H. International perspective on the diagnosis of death. *Br J Anaesth* 2012;108 Suppl 1:i14-28. https://doi.org/10.1093/bja/aer397.
27. Practice parameters for determining brain death in adults (summary statement). The Quality Standards Subcommittee of the American Academy of Neurology. *Neurology* 1995;45:1012-14. https://doi.org/10.1212/wnl.45.5.1012.
28. Bellomo R, Ronco C, Kellum JA *et al.* Acute renal failure – definition, outcome measures, animal models, fluid therapy and information technology needs: the Second International Consensus Conference of the Acute Dialysis Quality Initiative (ADQI) Group. *Crit Care* 2004;8:R204-12. https://doi.org/10.1186/cc2872.
29. Rady MY, Verheijde JL. Determining brain death after therapeutic hypothermia on nonpulsatile continuous-flow mechanical circulatory support devices. *J Cardiothorac Vasc Anesth* 2013;27:e8-9. https://doi.org/10.1053/j.jvca.2012.08.014.
30. NINCDS [National Institute of Neurological and Communicative Disorders and Stroke]. *The NINCDS collaborative study of brain death*, NINCDS monograph no. 24. Bethesda MD: U.S. Department of Health and Human Services.
31. Sołek-Pastuszka J, Biernawska J, Iwańczuk W *et al.* Comparison of two apnea test methods, oxygen insufflation and continuous positive airway pressure during diagnosis of brain death: final report. *Neurocrit Care* 2019;30(2):348-54 [published online 2018]. https://doi.org/10.1007/s12028-018-0608-7.
32. Sołek-Pastuszka J, Sawicki M, Iwańczuk W *et al.* Apnea testing using the oxygen insufflation method for diagnosis of brain death may compromise pulmonary function. *J Crit Care* 2018;44:175-8. https://doi.org/10.1016/j.jcrc.2017.10.038.
33. Setzer N. Brain death: physiologic definitions. *Crit Care Clin* 1985;1:375-96.
34. Salim A, Martin M, Brown C *et al.* Complications of brain death: frequency and impact on organ retrieval. *Am Surg* 2006;72:377-81. https://doi.org/10.1177/000313480607200502.
35. Escudero D, Otero J, Perez-Basterrechea M *et al.* Hyperthermia in brain dead patients. *Anaesth Intensive Care* 2015;43:269-70.
36. Wijdicks EFM, Manno EM, Holets SR. Ventilator self-cycling may falsely suggest patient effort during brain death determination. *Neurology* 2005;65:774. https://doi.org/10.1212/01.wnl.0000174626.94197.62.
37. Schwarz G, Errath M, Arguelles Delgado P *et al.* Ventilator autotriggering: an underestimated phenomenon in the determination of brain death. *Der Anaesthesist* 2019;68:171-6. https://doi.org/10.1007/s00101-019-0555-5.
38. Rossetti AO, Oddo M, Logroscino G, Kaplan PW. Prognostication after cardiac arrest and hypothermia: a prospective study. *Ann Neurol* 2010;67:301-7. https://doi.org/10.1002/ana.21984.
39. Haupt WF, Rudolf J. European brain death codes: a comparison of national guidelines. *J Neurol* 1999;246: 432-7. https://doi.org/10.1007/s004150050378.
40. Citerio G, Murphy PG. Brain death: the European perspective. *Semin Neurol* 2015;35:139-44. https://doi.org/10.1055/s-0035-1547533.
41. Guidelines for the diagnosis of brain death. Canadian Neurocritical Care Group. *Can J Neurol Sci* 1999;26: 64-6.
42. Flowers WM, Patel BR. Radionuclide angiography as a confirmatory test for brain death: a review of 229 studies in 219 patients. *South Med J* 1997;90(11):1091-6. https://doi.org/10.1097/00007611-199711000-00007.
43. Sinha P, Conrad GR. Scintigraphic confirmation of brain death. *Semin Nucl Med* 2012;42:27-32. https://doi.org/10.1053/j.semnuclmed.2011.07.007.
44. Ducrocq X, Hassler W, Moritake K *et al.* Consensus opinion on diagnosis of cerebral circulatory arrest using Doppler-sonography: Task Force Group on cerebral death of the Neurosonology Research Group of the World Federation of Neurology. *J Neurol Sci* 1998;159: 145-50. https://doi.org/10.1016/s0022-510x(98)00158-0.
45. Llompart-Pou JA, Abadal JM, Güenther A *et al.* Transcranial sonography and cerebral circulatory arrest in adults: a comprehensive review. ISRN *Crit Care* 2013; 2013:1-6. https://doi.org/10.5402/2013/167468.
46. Chang JJ, Tsivgoulis G, Katsanos AH *et al.* Diagnostic accuracy of transcranial Doppler for brain death confirmation: systematic review and meta-analysis. *AJNR Am J Neuroradiol* 2016;37:408-14. https://doi.org/10.3174/ajnr.A4548.
47. Poularas J, Karakitsos D, Kouraklis G *et al.* Comparison between transcranial color Doppler ultrasonography and angiography in the confirmation

of brain death. *Transplant Proc* 2006;38:1213-17. https://doi.org/10.1016/j.transproceed.2006.02.127.

48. Dominguez-Roldan JM, Jimenez-Gonzalez PI, Garcia-Alfaro C *et al.* Diagnosis of brain death by transcranial Doppler sonography: solutions for cases of difficult sonic windows. *Transplant Proc* 2004;36:2896-7. https://doi.org/10.1016/j.transproceed.2004.10.052.
49. Dupas B, Gayet-Delacroix M, Villers D *et al.* Diagnosis of brain death using two-phase spiral CT. *AJNR Am J Neuroradiol* 1998;19:641-7.
50. Sawicki M, Bohatyrewicz R, Safranow K *et al.* Computed tomographic angiography criteria in the diagnosis of brain death – comparison of sensitivity and interobserver reliability of different evaluation scales. *Neuroradiology* 2014;56:609-20. https://doi.org/10.1007/s00234-014-1364-9.
51. Frampas E, Videcoq M, de Kerviler E *et al.* CT angiography for brain death diagnosis. *AJNR Am J Neuroradiol* 2009;30:1566-70. https://doi.org/10.3174/ajnr.A1614.
52. Société Française de Neuroradiologie, Société Française de Radiologie, Agence de la Biomédecine. ['Recommendations on diagnostic criteria of brain death by the technique of CT angiography']. *J Neuroradiol* 2011;38(1):36-9. https://doi.org/10.1016/j.neurad.2011.01.001.
53. Bohatyrewicz R. Original protocol using computed tomographic angiography for diagnosis of brain death: a better alternative to standard two-phase technique? *Ann Transplant* 2015;20:449-60. https://doi.org/10.12659/AOT.893808.
54. Bohatyrewicz R, Sawicki M, Walecka A *et al.* Computed tomographic angiography and perfusion in the diagnosis of brain death. *Transplant Proc* 2010;42:3941-6. https://doi.org/10.1016/j.transproceed.2010.09.143.
55. Taylor T, Dineen RA, Gardiner DC *et al.* Computed tomography (CT) angiography for confirmation of the clinical diagnosis of brain death. *Cochrane Database of Systematic Reviews* 2014. https://doi.org/10.1002/14651858.CD009694.pub2.
56. Kramer AH, Roberts DJ. Computed tomography angiography in the diagnosis of brain death: a systematic review and meta-analysis. *Neurocrit Care* 2014;21:539-50. https://doi.org/10.1007/s12028-014-9997-4.
57. Sawicki M, Sołek-Pastuszka J, Chamier-Ciemińska K *et al.* Computed tomography perfusion is a useful adjunct to computed tomography angiography in the diagnosis of brain death. *Clin Neuroradiol* 2019;29:101-8. https://doi.org/10.1007/s00062-017-0631-7.
58. Sawicki M, Sołek-Pastuszka J, Chamier-Ciemińska K *et al.* Accuracy of computed tomographic perfusion in diagnosis of brain death: a prospective cohort study. *Medical Science Monitor* 2018;24:2777-85. https://doi.org/10.12659/MSM.906304.
59. Guideline three: minimum technical standards for EEG recording in suspected cerebral death. American Electroencephalographic Society. *J Clin Neurophysiol* 1994;11:10-13.
60. Facco E, Munari M, Gallo F *et al.* Role of short latency evoked potentials in the diagnosis of brain death. *Clin Neurophysiol* 2002;113:1855-66. https://doi.org/10.1016/s1388-2457(02)00259-6.
61. Gobert F, Dailler F, Fischer C *et al.* Proving cortical death after vascular coma: Evoked potentials, EEG and neuroimaging. *Clin Neurophysiol* 2018;129:1105-16. https://doi.org/10.1016/j.clinph.2018.02.133.
62. Schulz M, Iwersen-Bergmann S, Andresen H, Schmoldt A. Therapeutic and toxic blood concentrations of nearly 1,000 drugs and other xenobiotics. *Crit Care* 2012;16:R136. https://doi.org/10.1186/cc11441.
63. Bailey JM. Context-sensitive half-times: what are they and how valuable are they in anaesthesiology? *Clin Pharmacokinet* 2002;41:793-9. https://doi.org/10.2165/00003088-200241110-00001.
64. Huynh F, Mabasa VH, Ensom MHH. A critical review: does thiopental continuous infusion warrant therapeutic drug monitoring in the critical care population? *Ther Drug Monit* 2009;31:153-69. https://doi.org/10.1097/FTD.0b013e318196fb9f.
65. Bronchard R, Durand L, Legeai C *et al.* Brain-dead donors on extracorporeal membrane oxygenation. *Crit Care Med* 2017;45:1734-41. https://doi.org/10.1097/CCM.0000000000002564.
66. Beam WB, Scott PD, Wijdicks EFM. The physiology of the apnea test for brain death determination in ECMO: arguments for blending carbon dioxide. *Neurocrit Care* 2019;31:567-72. https://doi.org/10.1007/s12028-019-00784-7.
67. Bein T, Müller T, Citerio G. Determination of brain death under extracorporeal life support. *Intensive Care Med* 2019;45:364-6. https://doi.org/10.1007/s00134-018-05510-z.
68. Dragancea I, Rundgren M, Englund E *et al.* The influence of induced hypothermia and delayed prognostication on the mode of death after cardiac arrest. *Resuscitation* 2013;84:337-42. https://doi.org/10.1016/j.resuscitation.2012.09.015.
69. Rizvi T, Batchala P, Mukherjee S. Brain death: diagnosis and imaging techniques. *Semin Ultrasound CT MR* 2018;39:515-29. https://doi.org/10.1053/j.sult.2018.01.006.
70. Wujtewicz MA, Szarmach A, Chwojnicki K *et al.* Subtotal cerebral circulatory arrest with preserved breathing activity: a case report. *Transplant Proc* 2016;48:282-4. https://doi.org/10.1016/j.transproceed.2015.12.030.

71. Nakagawa TA, Jacobe S. Pediatric and neonatal brain death. Supplement to: Greer DM, Shemie SD, Lewis A *et al.* Determination of brain death/death by neurologic criteria. World Brain Death Project. JAMA. 2020 Sep 15;324(11):1078-97. Online Supplement 6 [at AMA Ed Hub]. https://doi.org/10.1001/jama.2020.11586.

72. Escudero D, Valentín MO, Escalante JL *et al.* Intensive care practices in brain death diagnosis and organ donation. *Anaesthesia* 2015;70:1130-9. https://doi.org/10.1111/anae.13065.

73. Magnus DC, Wilfond BS, Caplan AL. Accepting brain death. *N Engl J Med* 2014;370:891-4. https://doi.org/10.1056/NEJMp1400930.

74. Shewmon AD. The brain and somatic integration: insights into the standard biological rationale for equating 'brain death' with death. *J Med Philos* 2001; 26:457-78. https://doi.org/10.1076/jmep.26.5.457.3000.

75. Lane A, Westbrook A, Grady D *et al.* Maternal brain death: medical, ethical and legal issues. *Intensive Care Med* 2004;30:1484-6. https://doi.org/10.1007/s00134-004-2305-6.

76. Murphy PG, Smith M. Towards a framework for organ donation in the UK. *Br J Anaesth* 2012;108: Suppl 1:i56-67. https://doi.org/10.1093/bja/aer402.

77. Barber K, Falvey S, Hamilton C *et al.* Potential for organ donation in the United Kingdom: audit of intensive care records. *BMJ* 2006;332:1124-7. https://doi.org/10.1136/bmj.38804.658183.55.

78. Sprung CL, Truog RD, Curtis JR *et al.* Seeking worldwide professional consensus on the principles of end-of-life care for the critically ill. The Consensus for Worldwide End-of-Life Practice for Patients in Intensive Care Units (WELPICUS) study. *Am J Respir Crit Care Med* 2014;190:855-66. https://doi.org/10.1164/rccm.201403-0593CC.

Chapter 4. Family approach and consent/authorisation for *post mortem* organ donation

4.1. Introduction

Donation of organs and tissues from deceased persons saves lives, or significantly improves the quality of life of patients with end-stage organ failure. However, before donation can take place, consent to donation – or absence of any objection to donation – is needed, given either by the donor while alive (e.g. organ donor registry, organ donor card, non-donor registry, advance directives) or given by the family or legal representative of the potential donor [1-2]. The focus of this chapter is on the different legal systems for consent or authorisation to enable the donation of organs and tissues after death. Although the term 'consent' is used throughout this chapter, the Guide recognises that in some countries the term 'authorisation' rather than 'consent' is used to enable lawful procurement of organs and tissues.

This chapter also explains how the way of approaching the family to discuss donation opportunities varies, depending on the type of deceased donation procedure. It recognises that communication with bereaved family members requires clear and sensitive procedures or protocols, with donation opportunities discussed by appropriately trained specialists in donation, and it makes a number of recommendations as to how to communicate with families.

4.2. Consent or authorisation for organ and tissue donation

4.2.1. Legal consent systems

Consent for the donation of organs and tissues from deceased donors is subject to legislation and regulation in each country. In general, there are two main legal consent systems to express individual consent to organ donation: an opting-in system and an opting-out system. Although both systems are based on the self-determination of the individual, they have opposite starting points.

4.2.1.1. *Opting in or opting out*

According to the principle of the opting-in system, donation can only be initiated either if the deceased person in life explicitly expressed their willingness to donate, or when the qualifying bereaved family member gives consent. The opting-out system starts from the idea that it is legally defined as the norm and thereafter it is standard for people to donate organs *post mortem*, so organ donation takes place as long as there is no evidence of any objection (of legally accepted type) by the deceased person; note that some countries also accept evidence of previous oral objection by the deceased if the relatives present it. While an opting-out system presumes the consent for organ donation, the opting-in system states that donation can only take place after explicit consent. There are arguments for and against each system.

Table 4.1. **Legal provisions in European countries for consent to/authorisation of organ donation from deceased persons**

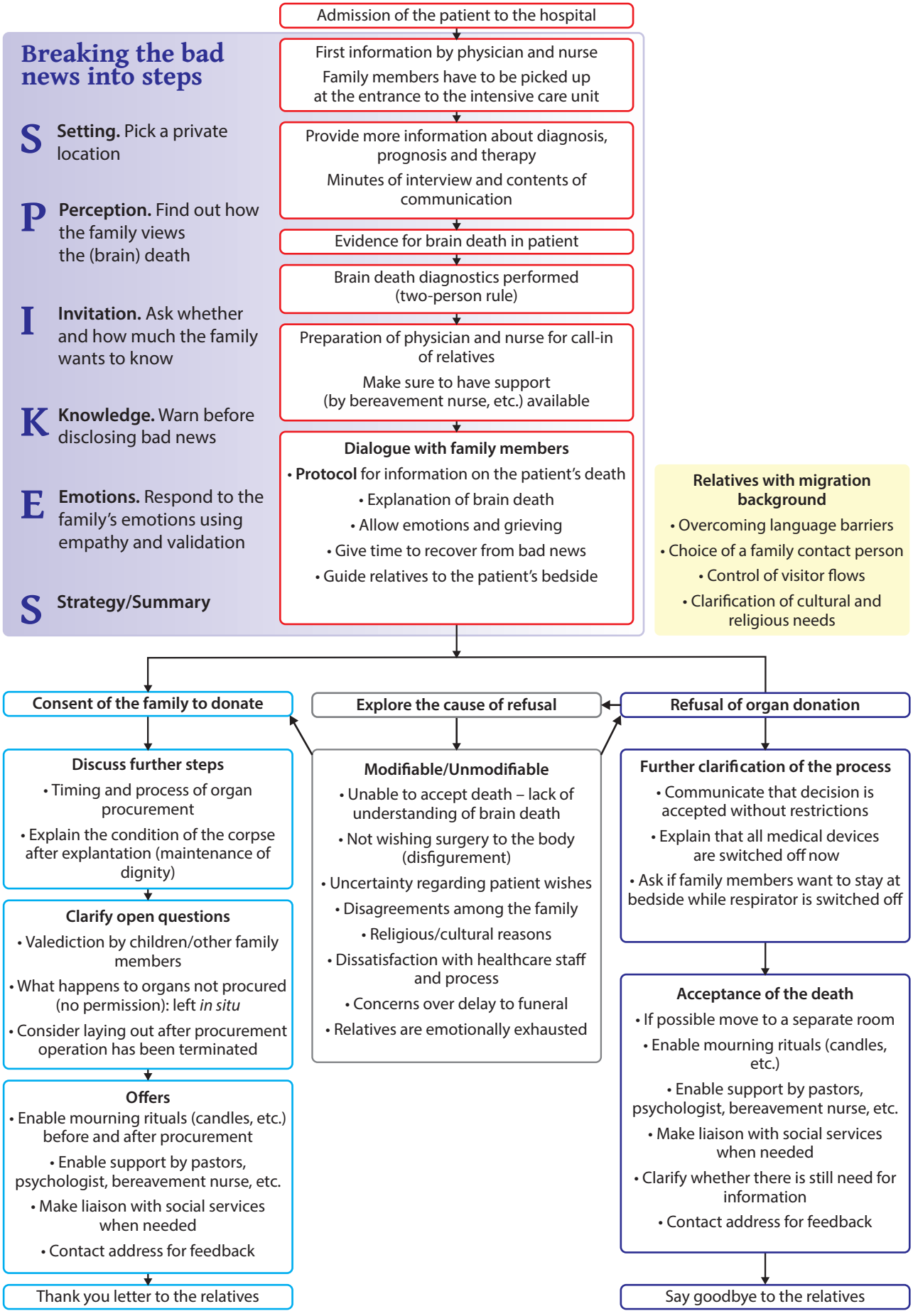
Country	National consent system	Donor registry	Non-donor registry
1 Armenia	opting-out		
2 Austria	opting-out		×
3 Belgium	opting-out	×	
4 Bosnia-Herzegovina	opting-out		
5 Bulgaria	opting-out		×
6 Croatia	opting-out		×
7 Cyprus	opting-in	×	
8 Czech Republic	opting-out		×
9 Denmark	opting-in	×	×
10 Estonia	opting-out	×	×
11 Finland	opting-out		
12 France	opting-out		×
13 Georgia	opting-in	×	×
14 Germany	opting-in		
15 Greece	opting-in	×	×
16 Hungary	opting-out		×
17 Iceland	opting-out		×
18 Ireland	opting-in		
19 Israel	opting-in	×	
20 Italy	opting-out	×	×
21 Latvia	opting-out	×	×
22 Lithuania	opting-in	×	×
23 Luxembourg	opting-out		
24 Malta	opting-in		×
25 Moldova	mixed system		
26 Montenegro	opting-in		
27 Netherlands	opting-out	×	
28 North Macedonia	opting-in	NA	NA
29 Norway	opting-out		
30 Poland	opting-out		×
31 Portugal	opting-out		×
32 Romania	opting-in	×	
33 Russian Federation	opting-out	×	×
34 San Marino	opting-out	NA	NA
35 Serbia	opting-out		×
36 Slovak Republic	opting-out		×
37 Slovenia	mixed system	×	×
38 Spain	opting-out	*	*
39 Sweden	mixed system	×	×
40 Switzerland	opting-in		
41 Türkiye	opting-in	×	
42 United Kingdom		×	×
a. England	opting-out		
b. Northern Ireland	opting-in		
c. Scotland	opting-out		
d. Wales	opting-out		

NA: data not available.

* Some countries do not have opting-in or opting-out registries, but this requirement is fulfilled by advance decisions (living wills) and/or registries that allow individuals to record their wishes about donation.

Source: Adapted from European Commission's implementation survey regarding Directive 2010/53/EU [5].

Figure 4.1. **Standardised sequence of dialogue with bereaved family of potential brain-dead organ donors (SPIKES) [12-13]**



From an ethical point of view, the two systems can be considered equivalent because each has systematic ways to express positive or negative intent. In practice, operational variations exist within both systems, especially related to the role of bereaved relatives. The role of the family in the decision-making process and when they should be informed depends on the prevailing legislation. It is good communication practice, and a sound basis for developing trust, to inform the family about donation in the most appropriate way and before donation proceeds if they are available. In some countries the law determines when the family should be informed about organ donation. From a practical point of view, the family is usually receiving detailed information at every stage during the treatment of a patient.

There are two subtypes of presumed (or deemed) consent system (opting-out): the 'soft' type of presumed consent means that the family is always asked about the opinion that the deceased person had expressed during their lifetime, which is most likely to be known by the relatives. In such cases, it is important to emphasise that we seek only the opinion expressed in the lifetime of the deceased. The 'hard' type of presumed consent means that only the deceased person's written objection can stop the process to donate organs (like the system in Austria). There is another important reason to contact the family before donation, in addition to finding out the deceased person's wishes about donation: in order to ensure or improve the quality and safety of organs for transplantation it is important to collate an accurate medical, social and travel history about the deceased. Finally, if there is no available clear evidence about the willingness or objection of the deceased, in practice the family has the most decisive role even in the case of legally defined presumed consent.

Considering the goal of not losing a donor for a communication reason, we have to keep in mind that open and exact communication with the family or the patient beforehand is the only right way to develop trust and create a positive attitude towards organ donation. Table 4.1 gives an overview of the different national consent systems in Europe. From the 44 responding countries, the majority (27 countries) have an opting-out system, while 15 countries reported an opting-in system and two a mixed system, where countries combine elements of both systems.

4.2.1.2. *Documenting people's decisions*

Irrespective of the type of consent system in place, many countries have developed the tools and mechanisms to allow citizens to record their decisions regarding posthumous organ donation alongside different activities to promote donation in general [3]. The most often used tools are donor cards and organ donor or non-donor registries that help make clear an individual's willingness or refusal to donate organs after death. People who have donor cards might be simultaneously recorded in the national donor registry.

In some countries, the personal statement on consent to donation recorded on a donor card contains (or can be amended to include) detailed information, e.g. consent to specific types of donation – donation after brain death (DBD) or donation after the circulatory determination of death (DCD) – or to the donation of specific organs or tissues. Such documents are called 'advance decisions (living wills)' or 'advance directives' and they are becoming popular in some countries. This system could enable people also to state prospectively under which medical conditions they do not want to receive life-sustaining therapy, and it does not conflict with the potential to become an organ donor.

National legislation or operational policies need to make clear what evidence (i.e., written or oral) is valid in their country to confirm consent or objection to organ and tissue donation. However, consent to donation can take many forms, and many countries allow more than one way to express wishes regarding organ donation. All national systems should enable individuals to withdraw their consent or objection at any time. This ensures that the most recent information about an individual's wishes is recorded in some way and is available 24/7 for a doctor or a donor co-ordinator who is involved in the donation process to check. Opting-in countries mainly have a donor registry, and opting-out countries have a non-donor registry, but several countries, such as Slovenia, use both registries.

4.2.2. Establishing consent in other circumstances

In countries with no legal framework for consent to donation, or where a potential donor (for example a minor) is not able to express their donation preference during their life, the decision is, as a rule, left to the family of the potential donor, based on the assumption that the family would respect and represent the potential donor's wishes. Alternatively, power to consent can pass to those who are the nominated legal representatives of the potential donor, according to the rules of the country.

In some specific cases, consent or authorisation to proceed with donation needs to be given by a coroner, judge or family court – for example, when

death occurs in suspicious circumstances or because of an illicit act.

In other circumstances, if the expressed wish of the person is to become a donor but the relatives of the potential donor are absent, or it is impossible to contact them, national procedures should enable organ and tissue donation where possible, providing there is sufficient medical, social and behavioural information available to support safe donation and transplantation.

4.2.3. Specific consent for deceased tissue donation

Consent for a deceased person's tissue donation should be obtained in accordance with legislation of the country where the patient dies, and internal hospital procedures should not differ from the rules applied to organ donation (see the *Guide to the quality and safety of tissues and cells for human application*). When the identity of the deceased donor is unknown, donation cannot take place, as consent and medical history will be impossible to obtain, and the presence of objection cannot be checked.

4.2.4. Documentation of consent

Consent for organ donation should be documented [4]. The method of documenting and record keeping should be described in a hospital's governance statutes in accordance with national rules (see Chapter 17). This documentation can prove that the personnel in charge obtained all mandatory information to legitimate organ donation after the declaration of death. This system has to be transparent and traceable.

4.2.5. Consent to deceased donation from non-residents

With increasing global mobility, the number of deaths of persons not residing permanently in the host country is likely to increase. These non-residents have the potential to become organ and tissue donors.

The diagnosis of death and the donation assessment (health, social, behavioural and travel history) of a potential non-resident donor will follow the law, regulations and requirements of the host country. The establishment of consent should be performed in accordance with the general rules described in this chapter as well as with the legal rules of the hosting country. There are countries where the family will be asked to consent to donation in the case of a potential donor coming from a foreign country. Another practice is to consult the country of origin of the (non-resident) potential donor through, for example, the competent authority or embassy, to ascertain the person's wishes in respect of organ donation (as recorded, for instance, in the national organ donor registry). An enquiry form (see Table 4.2) completed by both the host country and the country of origin might be helpful in establishing consent or objection. The embassy or other national representatives of a potential donor should be informed about organ donation.

Table 4.2. **Information needed in an enquiry form about possible organ donation from a non-resident**

Identification of the potential donor
• Family name, given name • Address • Date and place of birth • Passport number or personal identification number • Other useful information
Details of requesting organisation (host country) to donor's country of origin
• Organisation name • Address • Contact person • Contact details • Date/time
Record of response from potential donor's country of origin
• Consent to donation established – donation is possible • Objection to donation established – donation not possible • Contact person • Contact details • Date/time • Other useful information

4.3. Communication with family members involved in the donation process

Regardless of the circumstances, even in end-of-life care, the death of a potential donor is often sudden and unexpected. Communication with family members of the deceased may require multiple conversations with professional staff. The strategy must be to avoid unnecessary harm or distress. The best practice is to establish a stable relationship between family members and healthcare staff before the subject of organ donation is introduced. Skill enhancement of physicians has been advocated, to balance caring for grieving family members with raising the question of organ donation.

The following sections set out good practices in approaching families to enable a discussion about organ donation to take place at an appropriate time,

in an appropriate place and with someone with the appropriate skills [6-10].

4.3.1. Giving bad news

Bad news may be defined as 'any information which adversely and seriously affects an individual's view of their future' [11]. In the preparation phase of giving bad news, some questions must be answered: where, to whom, how and when to provide the news. The venue for discussion should help and support the conversation, perhaps located close to the place where their loved one died, to give family members the opportunity to say goodbye. It is important to provide a quiet, separate room for the family, where they can speak freely. It is also advisable to have resources that meet their minimum needs (telephone, handkerchiefs, water and seating).

It is frequently impractical to discuss organ donation with a large number of family members and it is recommended that participating family members should be limited to those who are key to the decision-making process, taking into account the legal framework in place and cultural practices or religious traditions. This should be explained to the other family members.

A supportive relationship is established by reflection of emotion and active listening. The empathetic response consists first of observation, looking for any emotion on the part of the relatives (silence, crying, denial, fear, anger); then help to express the emotion verbally; and then help to identify the cause of the emotion. Active listening is useful but is an underused communication technique; it involves asking questions to seek clarification, paraphrasing what has been said and the appropriate use of silence. To facilitate decision-making and bereavement that is uncomplicated by questions about brain injury and subsequent death, families need time to understand the information given, with care in the way and context that information was shared and attention to their emotional needs [12].

A Six-Step Protocol for Delivering Bad News (Spikes) is a model for giving bad news, which may be adapted from general medicine to approaching the family about donation [13]. It divides the task of giving the bad news into steps, rather than making it one big procedure that can be confusing. Each step represents an individual, learned and practised skill and the steps can then be put together into an overall package (see Figure 4.1).

The Nurse model can be used to structure the discussion (see Table 4.3) [14]. The basis for this approach to communication is to adapt the information to the relatives' capacity to take it in. It is about taking breaks, allowing reactions, expressing emotions and understanding. The formulation of respect for the situation of the relatives also serves the important purpose of strengthening their resources.

Table 4.3. **The NURSE model [14]**

1	**N**aming	Emotions	Name the perceived mood
2	**U**nderstanding	Understanding the emotions	Existing understanding expresses appreciation
3	**R**especting	Respect or recognition for the relatives	Opportunities to cope with the burden should be emphasised by the intensive staff
4	**S**upporting	Offer support to family members	In the form of an offer
5	**E**xploring	Find other aspects of emotion	Clarify ambiguous or missing feelings

The Nurse model provides a collection of helpful responses to the verbal or non-verbal emotions expressed by the affected person. The points are applied to specific situations, so they are not necessarily all applied each time or in the same order.

4.3.2. Importance and timing of the family discussion

The highly emotional conversations with relatives are a great challenge for doctors and nursing staff in emergency departments and intensive care units (ICUs).

The need for early identification of potential organ donors, combined with experience in practice, has highlighted the importance of the discussion with the family, which should be structured into a series of successive and independent phases [7]. The preparation for a family approach to organ donation starts when the patient is admitted to hospital, but the type of information delivered must follow the changes in the patient's condition. The relatives have to face, sometimes very soon, the possible consequence of devastating brain injury, and they will have many doubts, questions and fears to discuss. The emergency department and ICU staff must inform the family about all relevant and new information as soon as it is available, including all the diagnostic and therapeutic life-saving attempts.

The possibility of organ donation should never be presented until the family has understood and recognised the inevitability of the death of the potential organ donor [15]. It is very important to establish a

professional helping relationship that facilitates the necessary trust so that the relatives are willing to accept the option for donation [7].

Participation of the donor co-ordinator in the family discussion significantly increases the probability of obtaining consent; therefore the donor co-ordinator should be notified before the family discussion occurs. Consent rates may be higher when the interview takes place after the brain death declaration, or when brain death is expected to occur within the ICU, compared with other clinical situations [16].

The relatives of potential organ donors deserve a step-by-step approach, depending on the specific point in time when the discussion with the family happens, which should include:

a. development, progression and prognosis of the illness/critical injury, considering the initial diagnostic and therapeutic measures,
b. death after confirming brain-death diagnosis,
c. clarification of the expressed and presumed will of the deceased to organ donation,
d. information about the donation procedure.

Parallel to the mediation of medical and nursing specialist information, obtaining the empathetic support of relatives in the processing of these messages is a priority task of doctors and nurses.

4.3.3. Interprofessional task

In principle, discussions with relatives should be performed only by staff who have been trained to carry out such discussions. A doctor will be required to provide medical information. Caregivers, however, also have a decisive role to play in communicating with relatives, since they have the most intensive contact with the patient or their relatives. The conversation with the relatives is considered as an interprofessional task, because:

- relatives are in an extreme situation and grieving reactions can be better ameliorated by a team approach,
- the relationship and trust building between relatives and caregivers has often already taken place,
- the flow of information is guaranteed when the families turn to the nurses later.

If necessary, pastoral counsellors or clinical psychologists can be consulted. It is important to consider language barriers and to include translation services as required. Given the evolution of our domestic and global society, it is paramount to attend to the individual needs of families from diverse cultural backgrounds.

4.3.4. Dealing with grieving and aggressive reactions

Information about the sudden death of a beloved family member can lead to various grieving reactions among relatives, such as aggression and rage. The CALM model (in Table 4.4) as a communicative technique can offer a way out of difficult interactions [17].

Table 4.4. **The CALM model for de-escalation in dialogue with bereaved family members [15]**

Step 1	C – Contact	• Remain calm and matter-of-fact (do not get infected by the aggression of relatives) • Respect that the relative is in a difficult situation • Show friendly behaviour (verbal and non-verbal) • Admit possible own mistakes, without giving up justifications • Clarify relationships that have led to the unpleasant situation
Step 2	A – Appoint	• Directly address the emotions (anger, disappointment, etc.) shown by the relatives • Wait for a possible short-term escalation in the expression of emotions, wait before responding to aggression (anxiety, worry, etc.)
Step 3	L – Look ahead	• Clarify the professional relationship between doctor and patient • Suggest the option of choosing how to proceed • If necessary, define the limits and the communication rules with which further co-operation can take place
Step 4	M – Make a decision	• Offer a 'contract' that the family members can accept or not • Make alternative offers (if possible) • Postpone continuation of the discussion to a specific later date

Grief can be described as "a cognitive process of confronting a loss, of going over the events before and at the time of death, of focusing on memories and working toward detachment" [18].

Table 4.5. **Bereaved family and donor relatives' grief reactions to bad news**

Grief reactions	Remarks
Basics	Grief is a personal and unique experience. Healthcare professionals must respect the various displays of grief, taking into account unexpected emotions and behaviours. The sudden death of an apparently healthy person, which is frequently the case with a potential donor, finds the family unprepared. This extreme situation triggers a wide variety of reactions. All of them occur in combination with a variable degree of expression. This requires appropriate feedback to each individual reaction in order to avoid harm.
Shock	Shock is the initial reaction after receiving bad news. The person is unable to react and becomes emotionally paralysed. The person's non-response to the environment is an attempt at self-protection while being faced with uncontrollable feelings. This may be manifested in confusion (inability to assimilate information and/or to make decisions).
Denials and displacement	Denial and displacement are associated with lack of acceptance of an irreversible loss. Observed statements include 'It's impossible', 'It's not true', 'How could he have died, if he is breathing?' or 'You've made a mistake'. Relatives use denial as a protection against having to deal with reality. This requires patience, since forcing the information about reality only increases this defence mechanism in the family and further complicates adaptation to the new situation, or it may cause escalation of arguments and negative emotions on both sides with misunderstandings. This should be avoided. Inability to accept the loss of the loved one is often accompanied by a feeling of surrealism. This is stronger in cases of unexpected or sudden deaths. The emotional impact makes it difficult to assimilate information and increases the refusal to accept facts.
Anger and rebellion	When someone realises that a relative is dead, a feeling of undeserved harm and great injustice may arise. The typical reaction is anger and rebellion shown by asking such questions as: 'Why?', 'Why did he die?', 'Why did it happen to us?' In this early stage of grieving, relatives intensively look for an explanation for the reasons of death and may accuse medical staff. These reactions of the family, especially claims or allegations against a healthcare professional, are difficult to deal with. If the healthcare professional perceives them as threatening and tries to defend herself or himself, then it may be seen as confirmation of guilt. This should not be taken personally by the healthcare professional or the clinical team but seen as an essential part of the grieving process that might lead to an acceptance of death and an agreement to organ donation in time.
Rage and blame	Rage and blame are natural feelings born out of frustration when faced with the impossibility of changing what has happened. Therefore, this emotional thunderstorm should be allowed while the safety of relatives and clinical staff is ensured. It can be directed to the deceased, the medical team, God or even the person suffering. Rage and blame, when directed towards a healthcare professional, may be difficult to accept and cause confrontation. Blame is closely linked to rage. For the bereaved person, it may be necessary to find someone responsible for what has happened.
Bargaining	Another reaction is to negotiate the extension of a deceased person's life. This is described in the literature as 'bargaining'. In response to information about the death, the relatives try to deny the inevitability and irreversibility of this fact. They sometimes try to find a way to turn things round – 'If the brain is not working, isn't it possible to transplant the brain?' or 'To whom and how much do I have to pay, to make him alive?' Although sometimes a family's questions may cause impatience or indignation, it means that relatives are still willing to pay any price to regain the loved one.
Depression	Depression, as a short or long-lasting episode of disillusion, hopelessness, sadness and grief, is a common reaction to death. Depression is observed as 'family plunged into grief'. Relatives of the deceased are often withdrawn or submissive in conversation with clinical staff. They ask only a few questions. In comparison with a reaction of denial or anger, such muted behaviour or reaction from the family may seem to be an acceptance of death and organ donation. However, clinicians should proceed cautiously when observing such reactions because they are associated with increased risk of susceptibility to long-term trauma.
Acceptance	After some time, acceptance of death might be signalled. Reconciling oneself to the death of a close person usually occurs after an exhausting fight, when the family starts to think it is a 'better solution, than …'. Still they need to find a deeper meaning in the death and its circumstances, e.g. religious arguments or considerations such as 'Thanks to organ donation, the life of our relative is symbolically extended in a positive sense' or 'He died but his heart may save somebody's life', 'Although she suffered so much, she let someone else enjoy life', 'Though I lost my son, he let another mother still have her son thanks to the transplanted organ'. If relatives of a potential donor want to know who receives the donated organs, it can be said that they will be transplanted into a person 'similar' to the donor in the biological sense. This information may translate into a conviction of the meaningfulness of the gift.

The person leading the conversation with the family can meet with various emotional reactions that are characteristic of people in grief (see Table 4.5). It is very important to understand the possible reactions connected with grieving. For a conversation about potential organ donation, it is essential to establish good rapport with the relatives of the deceased. The donor co-ordinator is responsible for adjusting the conversation to the family's needs and expectations. This can be summarised as 'establishing a therapeutic relationship'.

The healthcare professional or donor co-ordinator who is leading the conversation with the relatives should respect their grieving. This type of conversation requires interpersonal skills, sensitivity and empathy. In situations when there is pressure on healthcare staff, the conversation with the family can become difficult, rushed or insensitive.

Table 4.6. **Aspects to consider in communicating with members of the potential donor's family**

Persons attending	Try to limit the number of family members who take part in the donation conversation to those who are legally allowed to make a decision on donation and family members who take the lead in the family network. Explain clearly to the other family members that the intention is to talk first with the key persons responsible, to simplify the communication process. If this is based on the social and cultural background of the donor family, most people will accept this, as long as they are informed properly. When there are social, cultural or language barriers or difficulties, consider seeking the support of interpreters or friends of the possible donor who have a greater level of understanding, integration or knowledge of religious references and whose co-operation may be beneficial for the family. These interpreters or friends should be previously informed about the donation, so they can support the family and maintain a favourable attitude, and not be limited to making a simple translation.
Place of conversation	The conversation should be carried out at the right time, in the right place by the right people. Proper preparation reduces the risk for errors, especially when important information is not available. The place of conversation should provide ease, and should be located close to the place where their loved one died, to enable sight of the deceased again and the chance to say farewell. It is important to provide the family with a quiet room, where they can speak freely and unobserved. They should be provided with at least basic needs (e.g. telephone, handkerchiefs, water and food).
Establishing good contact	Persons conducting conversations with families will encounter different emotional reactions (see Table 4.5). It is important to understand such mourning reactions. Further conversation about potential organ donation requires a good therapeutic relationship with the families.
Sensitivity and empathy	Everyone should respect the mourning of families. A check should be made whether organ donation is consistent with the will of the deceased person, in accordance with national regulations. This requires interpersonal skills, sensitivity and empathy, without psychological pressure, to avoid complications.
Family acceptance of organ donation	The conversation about organ donation aims to fulfil the will of the deceased donor and obtain the acceptance of the family of organ donation. Regardless of the legal position, acceptance of organ donation by relatives must be agreed, and this must not be achieved under pressure. Neither financial nor any material benefit can be offered, and nor can donation be conditional on the deceased donation being directed to a specific recipient or group of recipients.
Family refusal	The family has the right to express their opinion about organ donation, but the will of the deceased, expressed during life, should be respected if possible.

4.4. Approaching the family about donation after brain death

A multidisciplinary team should be responsible for planning the approach and discussing organ donation with the family. This allows all members of the team to be clear about how the discussion will proceed: when, where, with whom and what is going to be said. This multidisciplinary team should include the clinical team involved in the care of the potential donor, the donor co-ordinator and where necessary the local faith representative [8].

The team should determine:

a. any clinical issues to be clarified,
b. any evidence of the will of the deceased, such as registration on national donor registries, and next of kin or key family members to be involved in the consent process,
c. specific cultural needs and family or faith issues to be taken into account.

4.4.1. Information about brain death diagnosis

Irrespective of the consent system for organ donation, and differences in practice across countries [18-19], a conversation with the family of the potential DBD donor is required to convey information about brain death and the potential for organ donation [6].

The conversation with the family of a potential DBD donor will aim to do the following:

a. inform relatives of the patient's condition, including devastating brain injury, possible death, brain death testing and confirmation of death [20],
b. support the family by focusing on their emotions and current needs,
c. explain the current situation (with the concept of brain death and other aspects of death and donation),
d. inform relatives about the potential of donation, for which the timing is country-specific [20],
e. establish the wishes of the deceased about organ donation,
f. obtain additional information from relatives on medical, social and travel history and risk behaviours,
g. obtain family consent or support for organ donation.

Once the diagnosis of death using neurological criteria is established, the family should be informed in clear and simple words following the KISS rule (Keep It Short and Simple). Any questions about brain death, which can be difficult for medical non-professionals, must be answered objectively and

simply. In the conversation, it must be clear that the patient is dead. The word 'life' must be avoided. Keeping it short and simple means there is more time to meet the needs of the affected relatives.

Most ICU clinicians will not have received specific training in approaching the families of potential donors. Although the available evidence is conflicting, consent rates might be higher when donor co-ordinators are involved in family discussions [15, 21]. The donor co-ordinator should first ensure that the family understands what is meant by death as determined by neurological criteria. Only when the family understands that the patient has died – or that death is inevitable – should organ donation be discussed.

4.4.2. Information about organ donation

A conversation about organ donation aims to fulfil the will of the deceased and to obtain family consent or support for donation. Regardless of the legal position, such a conversation must aim to achieve an acceptance of organ donation by relatives. This acceptance cannot be forced or conditional, nor should it be achieved under pressure or by offering any financial or other material benefit.

It is difficult to proceed with donation when a family is strongly against it, even if there is evidence that their deceased family member wished to be an organ donor. The family has the right to express their opinion about organ donation, and clinicians need to make a balanced decision whether to continue with the donation without the support of the family – with the risk of damaging the emotional health of the relatives and possibly incurring bad publicity and a loss of public confidence in the organ donation programme – or whether to follow the wishes of the deceased and continue with the donation.

It might be helpful to use the following when discussing a refusal with the family [22]:

a. If the family claims that the deceased (or dying patient) did not agree to organ donation or had changed their mind, explore the basis on which the family gives such a statement.
b. When the family does not know anything about the attitude of the deceased to organ donation, discuss whether their deceased relative helped people generally, e.g. as a blood donor or by giving to charity, and how donation could help many people to benefit from a transplant.
c. If family members are concerned that the body will be disfigured, reassure them that the deceased's body will be fully respected and offer them the possibility of seeing their relative once the donation procedure has been completed.
d. In a case of religious concerns, offer a consultation with a religious leader or representatives.
e. In cases of dissatisfaction with the healthcare provided, record the complaints, but explain that the issue of organ donation should be kept separate.
f. Identify the persons involved in the refusal to donate and their role within the family, and attempt to communicate with them separately to understand and try to address their concerns.
g. Identify whether a disagreement to donation by individual family members is based on conflicts between family members, conflicts which can come to light when a person has died. In this case, try to separate the conflict from the issue of organ donation and bring the conversation back to what the individual would have wanted to happen.

It is helpful to ensure that, following organ donation, the family receives the appropriate care they need. In many countries, hospitals have dedicated bereavement teams to provide psychological support, access to social services, administrative support or religious counselling. The clinical team should establish whether there are any specific religious or spiritual requirements of the family and whether the family wishes to retain keepsakes such as locks of hair or tracing of the heartbeat, or hand and foot prints (usually of children). Finally, establish whether the family wishes to assist with the final preparation of the body following donation, such as washing or dressing in certain items of clothing.

Figure 4.1 provides a suggested sequence of family care and communication with family members, adapted from the Swisstransplant donation pathway [23]. Table 4.6 summarises some key aspects to consider during communication with potential donor family members.

4.5. Approaching the family about donation after the circulatory determination of death

4.5.1. The family in controlled donation after the circulatory determination of death

Any decision on the withdrawal of life-sustaining treatment (WLST) should be totally independent of any consideration of the potential

for controlled DCD (cDCD) (see Chapter 12). The guiding principle is that the decision on WLST is made in a transparent, consistent manner and independently of the intentions and plans for organ donation [24-27]. This eliminates any conflict of interest. No investigation focused on organ donation (including consent) can take place before a decision on WLST has been taken. However, it may not always be possible to separate discussions about WLST and donation, if the family members raise the issue of donation themselves. In such cases it must be clarified that the treatment of the patient and any decision about WLST must come first, before any discussion of organ donation.

Although cDCD cases naturally have to follow the same general donation principles with regard to consent, there are some differences and specificities of donation before death occurs. Usually families have a longer stay in the ICU, so there is a closer relation with ICU workers; normally the emotional shock is resolved because, when the consent for donation is going to be given, the fatal prognosis is assumed. We must be aware that donation is a possible situation, not a certain one, and families need to be informed about this.

It is vital that the family be fully involved in discussions about the cDCD process. In addition, the family must be given the following information:

a. reassurance that all healthcare at the end of life will be provided during the process,
b. the location where the withdrawal of treatment will be carried out,
c. the procedure after death diagnosis,
d. the expected time of death (the family need to be aware that the dying process could be prolonged),
e. the possibility that the person may not die within a timeframe consistent with organ donation,
f. reassurance that, if the timing of death prevents organ donation, then tissue donation will still be possible following death.
g. reassurance that, if the timing of death prevents organ donation, and tissue donation is to happen after death, the donor will be transferred to a room where the family can remain with the dying patient and where privacy will be provided.

4.5.2. The family in uncontrolled donation after circulatory death

General rules of consent for uncontrolled DCD (uDCD) are similar to those of DBD, applied according to national regulations. However, in the case of organ donation after irreversible cardiac arrest, more negative reactions of relatives might be expected, but obtaining acceptance of death might be easier because death is visible according to the traditional perception of death (the cessation of a heartbeat) when compared with DBD [28].

In uDCD, two different situations can be found:

a. The family was present when cardiopulmonary resuscitation (CPR) was performed.
In this situation the family sees all the efforts that have been made to save their relative's life, so this situation can lead to a better understanding of the patient's situation.
b. The family was not present when CPR was performed.
In this situation families do not know what care was given, and what was the real situation of their relative; the first information that they receive is about the relative's death.

Sudden death usually provokes strong reactions of denial, impotence or guilt, which requires understanding. During this first phase, donation should not be raised during the discussion, unless the family initiates talk about donation. This first discussion should be arranged in the emergency department, following the recommendations on good practice [15], e.g. in a private place, with staff allowing grief and accompanying the family to see their deceased relative. In this situation, clinical staff must be aware that the time available to introduce organ donation is shorter than for DBD.

4.6. Approaching the family about tissue donation

Conversations with the family on planned tissue donation (DBD and DCD) do not generally differ from the conversations related to organ donation, described above. Therefore, it is best practice to discuss donation of organs and tissues within one conversation with the family.

The experience of working with families suggests that some difficulties and possible opposition may occur in donation of tissues like skin, bones and eyes when family members may fear disfigurement of the body. In these situations, special emphasis should be put on the legal and medical obligations to respect the body's appearance. If necessary, some technical aspects of donation should be explained, for example the use of specific surgical incisions and sutures, or suitable prostheses or artificial eyes or bones. (See also Chapter 3, Recruitment of potential donors, identification and consent in the *Guide to the quality*

and safety of tissues and cells for human application, 4th edition).

4.7. Successful intercultural communication

4.7.1. Solutions to cultural and language problems

Because of the heterogeneous nature of migrant populations in Europe – in terms of language, social position, education, occupation, age, residence status, ethical and religious identities, economic conditions, family, friends and not least their individual experiences – the range of social realities, affiliations and identities within this group is enormous.

The transmission of bad news (diagnosis, prognosis, brain death, organ donation) is always difficult for the healthcare professionals. For those families with a migration background, additional factors such as family size, increased visitor frequency and language barriers require further preparation for the delivery of bad news. In extreme situations, cultural and religious factors are particularly important. Ultimately, this background can lead to a reduction in organ donation.

Clinical staff often underestimate the difficulty that laypeople can have in understanding information about hospital care. What applies in general also applies to people with an immigration background. Difficulties in communication with them are often attributed only to the lack of a common language. Above all, the mediation of emotional content and dealing with incriminating situations in the treatment of foreign-language relatives may demand new solutions, such as professional translation services. Only then can the information be correctly transmitted and the right questions be asked.

Cultural mediators must have:

- good oral language skills in two working languages,
- knowledge of translation technology,
- communication skills,
- knowledge of ethical guidelines,
- knowledge about cultural respect,
- ways of dealing with incriminating conversation situations,
- willingness to train regularly and, if necessary, to request supervision [29].

In contrast, individual relatives acting as interpreters can present a challenge. Ideally, it is best practice to work with educated interpreters who are familiar with the necessary terminology and who can explain and translate medical terms [30].

Frequently, patients with a migration background belong to large family groups with several generations. The close contact among family, kinship and friends gives each person individual support and security so that no one feels alone or isolated. In various cultures, the medical visit also represents a religious and social duty, which also explains the high number of hospital visits and long visits.

Since visitor flows in the ICU are a major problem, finding a family principal is recommended. Through accurate observation or in conversation, it will become clear who the family leader is. This main contact person is responsible for the regulation of visitor flows, the transfer of information to the family circle and so on.

Table 4.7. **Issues and solutions in family members' care**

Issue	Solutions
Overcome language barriers	• Clarify possible language barriers • If a member of the family does not sufficiently speak the language of the country, an interpreter or a colleague who is a native speaker must be consulted
Choose central family contact person	• Clarify who is the family principal partner (family head, family interpreter) • Forward all information about the patient's health to the contact person, who then informs the family group
Clarify if patient belongs to a faith community	• The faith and the religious rituals must be determined • Clarify whether a religious representative should be consulted
Control visitor flows	• Make arrangements and assume responsibility (visitor flows, number of visits, attendance) • Clarify that the time window for visits is restricted by the needs of intensive care unit (ICU)/rest for the recovery of patients • Lay out condolence books for visitors (relatives, friends, etc.) to document their participation
Respect cultural and religious differences	• Respect religious norms and values, as far as compatible with operation at the ICU • Create opportunities for prayer and meditation • Offer farewell facility to the relatives

Source: Development of this model in the Intercultural Workshop of the Austrian Public Health Institute [27].

After clarification of possible problem areas, family members' care can be directly linked to the SPIKES (Figure 4.1), NURSE (Table 4.3) and CALM (Table 4.4) models.

When there are social, cultural or language barriers or difficulties, the support of interpreters or friends of the potential donor with a greater level of integration or knowledge of religious beliefs may be beneficial for the family. These persons should be previously informed about donation, so that they can support the family and also champion a favourable attitude towards donation, rather than be limited to making a simple translation. The conversation should be planned, and then carried out at the right time, in the right place by the right people. Proper preparation for the conversation reduces the need for improvisation and the likelihood of errors [31-33].

4.7.2. Religious-cultural aspects in the organ donation process

Aside from race/ethnicity, religion plays a key role for many people in their decision whether to become an organ donor. Although all major religions support organ, tissue and eye donation, within each religion there are different schools of thought. Most religious texts allude to the concept of helping the needy, which can be extrapolated to include organ donation [34].

There is a general consensus in the major religions that:

- organ donation is an act of charity,
- everyone should make a personal decision during their lifetime for or against deceased organ donation,
- a just distribution of donor organs is necessary,
- organ trafficking is rejected,
- relatives should be involved in the decision about organ donation.

Whether brain-death diagnosis and organ donation are accepted in individual cases depends on the personal, religious and ideological attitudes of the relatives and on their cultural connections. If during the lifetime of the deceased no written declaration of intent has been made, the oral or the supposed will of the deceased should be ascertained in the family discussion.

There is no Europe-wide religious statement from churches on organ donation, but each country may have or should ask for statements from all existing religious groups [34]. The Christian churches accept the death of the brain as a defined death of humans and describe organ donation as an act of charity. In some other religions and cultures, brain death and the ethical basis of organ donation are controversial, or even rejected [35].

This is also the reason why ICU professionals are met with incomprehension and contradiction from relatives with other cultural-religious backgrounds, regarding both the acceptance of observed brain death and the acceptability of organ donation [36].

It is crucial to know the religion, culture and world view of patients and their relatives in order to minimise possible conflicts.

4.7.3. Recommendations in response to religious-cultural aspects of organ donation

We cannot be prescriptive about people's faith, beliefs, values and traditions, which are unique to each individual. The overarching aim of the hospital staff who are in conversation with the family is to identify and meet these unique needs as part of the routine person-centred care at the end of life. We should first ask of the family, from a place of curiosity, empathy and humility, 'I know how important it is for families to make a decision in a way that honours their faith, beliefs, values and traditions, and I want to be able to support you at this time by understanding as much as I can about your faith and beliefs, so please help me understand: what is important for you right now?'

Taking into account the main factors that influence the moment of donation, which are language barriers, absence of donation culture in the country of origin, refusal to donate because of a belief that their religion prohibits it, rejection of donation because they think that this will prevent the performance of their funeral rituals and lastly difficulties in family communication, often due to remoteness, it is recommended to:

- develop information and awareness programmes on donation and transplantation aimed at migrant populations to be able to achieve their full integration into the process,
- promote collaboration between the transplant network and cultural mediators, defining their role within transplant co-ordination and training them adequately,
- strengthen relationships with the most representative social organisations of different groups,
- ensure specific training for cultural mediators and translators.

4.8. Communication training

The training of all professionals – doctors, nurses, co-ordinators and staff from the ICU, especially those who are involved in family interviews, communication of bad news and discussion of organ donation – is essential [37]. Their skills in verbal and non-verbal interpersonal communication are vital in establishing a relationship with the family. It is also important for the professionals involved to receive specific training to help them avoid the emotional overload that this type of work may induce.

It is recommended that hospital quality systems in organ donation should promote specific communication training of professionals in critical care units through continuing professional education.

The basics and techniques of interviewing must be offered during training through practical exercises, including simulated exercises such as breaking bad news, dealing with the fears and grief of relatives and dealing with dying, death and organ donation. It is helpful to use specialised, trained actors to take on the role of family members in specific situations. The feedback of the member–actor, doctor and nurse will provide effective and fundamental learning to overcome any conflicts in the organ donation process.

4.9. Conclusion

The sudden death of a family member is associated with profound sadness, insecurity and anxiety. This makes communication with the relatives a challenge for doctors and nurses. In addition to medical expertise, social and emotional skills are also required. This chapter has set out the key mechanisms for establishing consent – or at least minimising the refusal rate for organ and tissue donation – and for communication with bereaved families. It also recognises the specific skills required to respond to the issues raised by families.

Research agenda

From the literature and discussion of the available evidence, several topics have been identified for which evidence is inconsistent, insufficient or non-existent. The authors of this guide recommend that future research, where possible in well-designed randomised clinical trials, should focus on the following research gaps:

1 Role of families in decision-making and debriefing.
2 Identification of factors that influence a positive or negative decision regarding organ donation.
3 Qualitative research on the experience of professionals discussing donation opportunities with relatives of potential deceased donors.
4 Qualitative research on the experience of families who have been approached to discuss donation opportunities.
5 Evaluation of the impact that organ donation has on the grieving process of families.

4.10. References

1. WHO Guiding Principles on Human Cell, Tissue and Organ Transplantation, available at www.who.int/transplantation/en/, accessed 7 May 2021.
2. Additional Protocol to the Convention on Human Rights and Biomedicine concerning Transplantation of Organs and Tissues of Human Origin, available at http://conventions.coe.int/treaty/en/Treaties/Html/186.htm, accessed 7 May 2021.
3. Rosenblum AM, Li AH, Roels L *et al.* Worldwide variability in deceased organ donation registries. *Transpl Int* 2012;15:801-11.
4. Project Odequs (Organ Donation European Quality System), available at www.odequs.eu, accessed 7 May 2021.
5. Study on the uptake and impact of the EU Action Plan on Organ Donation and Transplantation (2009-2015) in the EU member states: Factor Study, available at https://ec.europa.eu/health/sites/health/files/blood_tissues_organs/docs/2017_euactionplan_2009-2015_impact_en.pdf, accessed 7 May 2021.
6. Valero R, ed. *Transplant coordination manual*, 3rd edition. Barcelona: Aguiló grafic, 2014. ISBN 978-87-616-8840-1.
7. Organización Nacional de Trasplantes. *Good practice guidelines in the process of organ donation*. Madrid: ONT, 2011, available at www.ont.es/publicaciones/Documents/VERSI%C3%93N%20INGLESA%20MAQUETADA_2.pdf, accessed 7 May 2021.
8. Nice (National Institute for Health and Clinical Excellence). *Organ donation for transplantation: improving donor identification and consent rates for deceased organ donation 2011*, available at www.bts.org.uk/Documents/Publications, accessed 7 May 2021.
9. Witjes M, Jansen NE, van Dongen J *et al.* Appointing nurses trained in organ donation to improve family consent rates. *Nurs Crit Care* 2019 Jul 11. https://doi.org/10.1111/nicc.12462.
10. Shaw D, Gardiner D, Lewis P *et al.* Conscientious objection to deceased organ donation by healthcare professionals. *J Intensive Care Soc.* 2018 Feb;19(1):43-7. https://doi.org/10.1177/1751143717731230. Epub 2017 Sep 14.
11. Buckman R. *Breaking bad news: a guide for health care professionals*. Baltimore: Johns Hopkins University Press, 1992:15.

12. Sque M, Long T, Payne S. Organ donation: key factors influencing families' decision-making. *Transplant Proc* 2005;37:543-6.
13. Baile WF, Buckman R, Lenzi R *et al.* SPIKES – a six-step protocol for delivering bad news. *Oncologist* 2000;5:302-11.
14. Back AL, Arnold RM, Baile WF *et al.* Efficacy of communication skills training for giving bad news and discussing transitions to palliative care. *Arch Intern Med* 2007;167(5):453-60.
15. Domínguez-Gil B, Murphy P, Procaccio F. Ten changes that could improve organ donation in the intensive care unit. *Intensive Care Med* 2016 Feb;42(2): 264-7. https://doi.org/10.1007/s00134-015-3833-y. Epub 2015 May 19.
16. Domínguez-Gil B, Coll E, Pont T *et al.*, en representación del Consorcio ACCORD-España. End-of-life practices in patients with devastating brain injury in Spain: implications for organ donation. *Med Intensiva* 2017 Apr;41(3):162-73. https://doi.org/10.1016/j.medin.2016.07.011. Epub 2016 Oct 25.
17. Schweickhardt A, Fritzsche K. *Kursbuch ärztliche Kommunikation. Grundlagen und Fallbeispiele aus Klinik und Praxis*. Köln: Deutscher Ärzte-Verlag, 2009.
18. Stroebe M, Schut H. The dual process model of coping with bereavement: rationale and description. *Death Stud* 1999;23(3):197-224.
19. Jansen NE, McDonald M, Haase-Kromwijk B *et al.* When are bereaved family members approached for consent to donation? Commentary from ten European member states. *Organs, Tissues & Cells* 2014;17: 101-13.
20. Danbury C, Barber V, Collett D *et al.* Effect of "collaborative requesting" on consent rate for organ donation: randomised controlled trial (ACRE trial). *BMJ* 2009;339:899-901.
21. Shaw D, Georgieva D, Haase B *et al.* Family over rules? An ethical analysis of allowing families to overrule donation intentions. *Transplantation* 2017 Mar;101(3): 482-7. https://doi.org/10.1097/TP.0000000000001536.
22. Swisstransplant and Comité National du don d'organes. *The Swiss Donation Pathway, Modul V, Familienbetreuung und Kommunikation*. Berne: Swisstransplant and Comité National du don d'organes, 2014, available at www.swisstransplant.org/fileadmin/user_upload/Infos_und_Material/Swiss_Donation_Pathway/SDP_modul_5_Familie_Kommunikation_DE_2014.pdf (in German), accessed 7 May 2021.
23. Organización Nacional de Trasplantes. *Donation after circulatory death in Spain: current situation and recommendations*. National consensus document, 2012 (in Spanish), available at www.ont.es/infesp/Paginas/DocumentosdeConsenso.aspx, accessed 7 May 2021.
24. British Transplant Society. *Donation after circulatory death*, available at www.bts.org.uk/Documents/Guidelines, accessed 7 May 2021.
25. National recommendations for donation after circulatory death in Canada. *CMAJ* 2006;175(8):S1-S24.
26. Bernat JL, D'Alessandro AM, Port FK *et al.* Report of a national conference on donation after cardiac death. *Am J Transplant* 2006;6:281-91.
27. Andrés A, Morales E, Vázquez S *et al.* Lower rate of family refusal for organ donation in non-heart-beating versus brain-dead donors. *Transplant Proc* 2009;41:2304-5.
28. Dagmar D. *Transkulturelle Kompetenz. Lehrbuch für Pflege-, Gesundheits- und Sozialberufe*. Bern: Verlag Hans Huber, 2007.
29. Gerish K, Chau R, Sobowale A, Birks E. Bridging the language barrier: the use of interpreters in primary care nursing. *Health Soc Care Community* 2004;12(5): 407-13.
30. Haddow G. Donor and nondonor families' accounts of communication and relations with healthcare professionals. *Prog Transplant* 2004;14:41-8.
31. Jacoby LH, Breitkopf CR, Pease EA. A qualitative examination of the needs of families faced with the option of organ donation. *Dimens Crit Care Nurs* 2005;24:183-9.
32. Sanner MA. Two perspectives on organ donation: experiences of potential donor families and intensive care physicians of the same event. *J Crit Care* 2007;22: 296-304.
33. Schleicher B. Professionelle interkulturelle Kommunikation im Angehörigengespräch ['Intercultural communication by healthcare professionals when talking to relatives']. Development of this model in document presented at Interkulturelle Herausforderung Organspende 2018 [the Intercultural Workshop of Gesundheit Österreich].
34. Wijdicks EFM. Brain death worldwide accepted fact but no global consensus in diagnostic criteria. *Neurology* 2002;58(1):20-25.
35. Deutscher Ethikrat. *Hirntod und Entscheidung zur Organspende*. Berlin: Stellungnahme, 2015.
36. Oliver M, Woywodt A, Ahmed A, Saif I. Organ donation, transplantation and religion. *Nephrol Dial Transplant* 2011;26:437-44.
37. Witjes M, Jansen NE, van der Hoeven JG *et al.* Interventions aimed at healthcare professionals to increase the number of organ donors: a systematic review. *Crit Care* 2019 Jun 20;23(1):227. https://doi.org/10.1186/s13054-019-2509-3.

Chapter 5. Management of the potential donor

5.1. Introduction

The irreversible loss of the entire functions of the brain, as the consequence of a devastating brain injury, is responsible for pathophysiological effects and clinical conditions that should be promptly identified and treated.

Aggressive donor management (ADM) protocols include early identification of possible donors, management at the intensive care unit (ICU) by dedicated personnel and early, aggressive use of fluid resuscitation, vasopressors and hormone therapy. Implementation of standardised ADM protocols gives priority to the management of all critically brain-injured patients identified as possible organ donors, allowing for a timely determination of death determined by neurological criteria, or brain death (BD). ADM protocols result in increased numbers of organs procured per donor [1]. Therefore, ADM is an essential component of the process of donation after brain death (DBD).

Organ-protective intensive care therapy is the first step towards successful and durable transplantation. To protect organs intended for transplantation from damage and to maintain functional organ quality at the time of procurement, optimal therapy should be based on specific targets and well-defined donor-management goals, particularly in the case of extended criteria donors (see Chapter 7) [2-8]. The basic standards of appropriate intensive care medicine and therapy aimed at saving a patient's life already include all aspects of ADM protocols and organ-protective intensive care therapy after BD, providing continuous protection to any tissue or organ [9].

5.2. Pathophysiological changes caused by brain death

Significant brain injury of any aetiology causes the onset of a systemic pro-inflammatory response syndrome (SIRS) prior to the occurrence of BD. Typical effects of SIRS are leukocyte mobilisation and release of inflammatory mediators, generation of reactive oxygen mediators, increased vascular permeability and organ dysfunction. BD also creates a variety of inflammatory, haemodynamic and endocrine effects, which may lead to significant organ injury prior to organ procurement.

BD causes a typical haemodynamic pattern with consecutive dysregulation as a result of the loss of central control of the cardiovascular system, the respiratory command, the baro- and chemoreceptors and the hypothalamic-pituitary axis. The pathophysiological changes evolve in two phases:

a. The agonal period occurring just before BD, a period which is characterised by a catecholamine surge (autonomic storm) responsible for transient episodes of tachycardia–tachyarrhythmias and hypertension: a physiological response to maintain cerebral and coronary perfusion, associated with redistribution of regional blood flow, increased afterload and visceral ischaemia/injury.

b. The agonal period is followed by the cessation of central regulatory mechanisms as soon as

residual brain-stem functionality disappears because of the gradual arrest of central sympathetic adrenergic regulation.

As a consequence of the irreversible loss of brain function, the most common clinical pattern in BD patients is [10] a combination of:

a. haemodynamic instability and cardiovascular dysfunction, caused by gradual cessation of central sympathetic adrenergic cardiovascular regulation, which is often compared to a sepsis-like or post-cardiac arrest syndrome due to the inflammatory response (up-regulation of pro-inflammatory cytokines) and ischaemia–reperfusion phenomena,
b. hypothermia due to the loss of hypothalamic thermoregulation,
c. the development of central diabetes insipidus as a result of hypothalamic-pituitary-axis loss of function,
d. reduced CO_2 production due to decreased metabolic activity.

These effects should be promptly and aggressively treated, to diminish the damage to organs that could be procured for transplantation. Cardiovascular, pulmonary and metabolic management form the cornerstones of potential organ-donor management. To achieve the goals of optimal donor care, the use of comprehensive monitoring and close observation of the donor is necessary.

Treatment regimens of the potential DBD donor should consider the following pathophysiological changes:

a. Catecholamine surge or burst (autonomic storm), which occurs during the short period just before BD and is characterised by:
i. hypertension,
ii. tachyarrhythmias,
iii. pulmonary oedema,
iv. raised vascular resistance,
v. disseminated intravascular coagulation,
vi. restricted capillary functions,
vii. myocardial dysfunction.

b. The cessation of central regulatory mechanisms, which occurs as soon as residual brain-stem functionality disappears, is characterised by:
i. reduced cardiac output,
ii. hypovolaemia,
iii. hypotension,
iv. hypokalaemia,
v. hypernatraemia,
vi. hypothermia,
vii. hypocapnia,
viii. diffuse inflammatory response,
ix. diabetes insipidus.

Therefore it is important to:

a. detect and correct hypovolaemia, reduced cardiac function, reduced systemic vascular resistance,
b. detect and correct metabolic and endocrine abnormalities, e.g. hypernatraemia, hypokalaemia, blood glucose abnormalities,
c. prevent hypothermia.

Table 5.1. lists the incidence of the most common physiological derangements that are associated with BD.

Table 5.1. **Common physiological derangements associated with brain death**

Derangement	Incidence %
Hypotension	81
Diabetes insipidus	65
Disseminated intravascular coagulation	28
Cardiac arrhythmias	25
Pulmonary oedema	18
Metabolic acidosis	11

Source: FA Hensley, DE Martin, GP Gravlee. *A practical approach to cardiac anesthesia*. 5th edition (23 October 2012) [8].

5.3. Monitoring and target parameters

Organ-protective intensive care therapy based on standardised critical care end-points (see Table 5.2) aims to achieve an increase in both the quality and the number of transplanted organs [10].

Basic monitoring (pulse oximetry, invasive arterial pressure, central venous pressure (CVP), core temperature, urinary output) is not enough whenever the potential donor is haemodynamically unstable or when a thoracic organ may be considered for transplantation: in these cases, additional parameters (see Table 5.3) should be monitored, using any of three methods – echocardiography, minimally invasive cardiac output monitoring or pulmonary artery catheterisation – to improve the quality and the number of utilised organs [11].

Table 5.2. **Basic monitoring parameters in critical care and target ranges in adults**

Basic parameters	Target range (adults)	Suggested frequency of monitoring
Central body temperature	36 °C to 37 °C *	Continuously
Invasive mean arterial pressure (MAP)	60-75 mmHg	Continuously
Heart rate **	70-100/min **	Continuously
Urine output	0.5 to 1.5 mL/kg/h	Hourly
Central venous pressure (CVP)	6–12 mmHg	Continuously
Peripheral arterial oxygen saturation (SpO_2)	> 95 %	Continuously
Arterial blood gas, pH	7.35–7.45	Every 2 to 4 hours or as needed
Na	135–145 mmol/L	Every 2 to 4 hours or as needed
K	3.5–4.5 mmol/L	Every 2 to 4 hours or as needed
Blood glucose	< 180 mg/dL (8.3 mmol/L)	Every 2 to 4 hours or as needed
Plasma biochemistry, urine sediment, C-reactive protein		Every 12 hours or as needed
Calcium level	Normal range	Every 2 to 4 hours or as needed
Haemoglobin	≥ 7 g/dL (≥ 4.4-5.6 mmol/L)	Every 6 hours or as needed
Platelets	> 50 G/L	Every 12 hours or as needed
Prothrombin time/partial thromboplastin time	within acceptable range to avoiding bleeding †	Every 12 hours or as needed
Magnesia level	Normal range	Every 12-24 hours

Notes:

* Mild hypothermia (34 to 35 °C) may be considered to reduce the rate of delayed graft function in kidney recipients of organ donors after brain death [12].

** Due to failure of the vagus node, sinus tachycardia will be observed; if there are no actual or expected cardiac complications, heart rates up to 120/min can be accepted, especially when inotropes or catecholamines are applied.

† Reference range depends on methods of measurement as well as type of documentation of coagulation parameters; this varies between countries and therefore must be checked locally with the target documented.

Regular evaluation of the fluid balance (input–output) and laboratory monitoring of urine gravity and ionograms (both on plasma and urine samples) are required to ensure electrolytic balance. Further revaluation should be done according to the donor instability; however, for potential lung donors, PaO_2/FiO_2 should be checked at least every 4 hours and recruitment manoeuvres should be performed hourly from BD until organ procurement [13-14].

Table 5.3. **Additional monitoring parameters in haemodynamically unstable donors and in donors of thoracic organs**

Additional parameters	Target range
Cardiac index	2.0-5.0 L/min/m^2
Stroke volume index	40-60 mL/m^2
Pulmonary arterial occlusion pressure	< 12 mmHg
Systemic vascular resistance index	2000 ± 500 dyn × s/cm^5/m^2
Intra-thoracic blood volume index	850-1000 mL/m^2
Extravascular lung water index	3-7 mL/kg
Central venous oxygen saturation ($ScvO_2$) %	70 %

5.4. Specific considerations

5.4.1. Hypotension due to hypovolaemia and fluid replacement

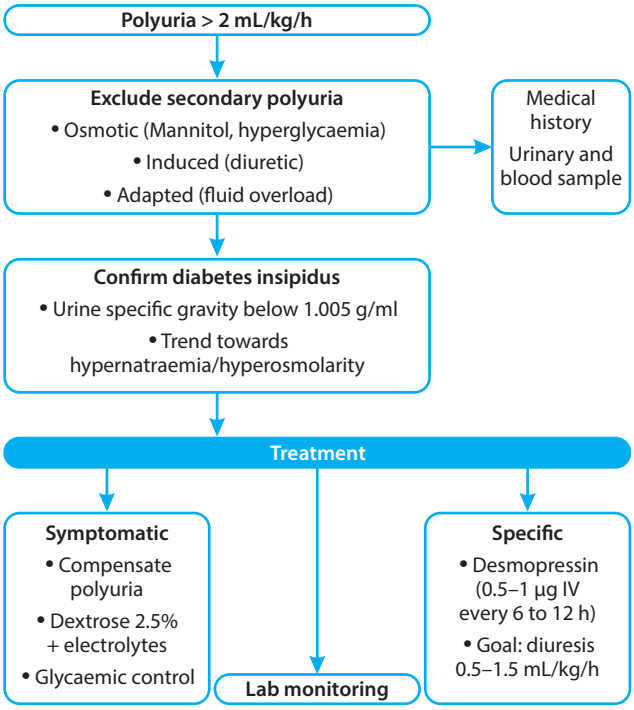
Hypovolaemia, absolute or relative, is frequent in BD because of the cessation of central stimulation of the vascular bed and up-regulation of pro-inflammatory cytokines. Large volumes of fluid replacement may be necessary to stabilise the circulatory system and to maintain organ perfusion. The choice of i.v. fluids and the rate of administration should also take into account any volume restrictions or prior dehydrating measures to treat cerebral oedema or cardiac complications before BD, as well as uncontrolled diabetes insipidus (DI). Measures should be taken to evaluate the response to fluid resuscitation and to avoid fluid overload effects on the respiratory system, guided by a monitoring system ensuring the precise haemodynamic profile and left ventricular filling pressure.

Administration of crystalloids or colloid solutions aims to correct intravascular deficit. If large volumes of crystalloid solutions are given, balanced salt solutions may help avoid hyperchloraemic acidosis.

There are still controversies about the use of hydroxyethylamidons in case of distributive shock. According to some authors, new-generation rapidly degradable hydroxyethyl starch solutions with a low degree of substitution seem to have less

risk of nephrotoxicity (osmotic nephrosis) on donor kidneys and can be administered with a restriction of maximal dose of 33 mL/kg/day on the first day and 20 mL/kg/day on subsequent days. This complication was initially described with the first-generation hydroxyethylamidons in DBD kidney donors [15-17]. The European Society of Intensive Care Medicine (ESICM) recommends colloids not be used in patients with head injury, and gelatins and hydroxyethyl starch not be administered in organ donors [18]. Though this issue is currently the focus of considerable debate, the use of colloids may be acceptable as bolus infusion to resolve as quickly as possible maintained hypotension [19]; several ongoing trials are likely to provide new data in the very near future – until then, colloids are usually not recommended in organ donors.

Figure 5.1. **Management of polyuria in the potential donor after brain death**



Source: Cheisson G, Duranteau J. Modalités de la prise en charge hémodynamique [21].

Competing requirements for organ perfusion may produce antagonistic strategies such as fluid replacement or a high value of positive end-expiratory pressure (PEEP). Attentive bedside multi-organ donor management supports adequate perfusion to vital organ systems even with CVP < 6 mmHg. A strict fluid balance can avoid volume overload, increasing the rate of lung grafts available for transplantation without impacting either kidney graft survival or the rate of delayed graft function [20].

5.4.2. Endocrine management

5.4.2.1. *Central diabetes insipidus*

Central DI is commonly observed (approximately 65 % of DBD donors). Its management should be initiated promptly, as shown in Figure 5.1 [21]. DI is caused by a lack of anti-diuretic hormone (ADH) produced by the hypothalamic-pituitary axis. DI is characterised by polyuria, with a urine volume > 2 mL/kg/h, urine specific gravity of < 1.005 and development of hypernatraemia. Also hypokalaemia can occur. Untreated, this pathology causes rapid and significant fluid loss (water deficiency) and a severe electrolyte imbalance (especially hypernatraemia) [2, 4-5, 7, 22-23].

Treatment of central DI (see also Figure 5.1) includes the following steps [22]:

a. Anti-diuretic hormone replacement: first-line medication is desmopressin (1-4.0 µg intravenous bolus)

i. If there is a marked decrease of diuresis (possible anuria), a lack of fluid volume is likely and fluid balance must be restored. There is no indication for the application of diuretics.

ii. In persistent polyuria, the blood sugar level must be checked to exclude osmotic diuresis (and corrected if necessary) before further administration of desmopressin.

iii. Repeated titrated application of desmopressin is necessary if symptoms of DI recur. As an alternative to desmopressin, vasopressin may be continuously administered at a dosage of 0.8-1 IU/h (anti-diuretic effect).

b. Sufficient fluid volume replacement, with mandatory monitoring of electrolyte and blood glucose levels:

i. In cases of hypernatraemia with hypovolaemia, water should be administered via a nasogastric tube, and intravascular volume should be restored with isotonic sodium chloride prior to water-deficits correction by 5 % glucose solution combined with insulin, while monitoring blood glucose levels.

ii. In cases of hypernatraemia without fluid depletion, administration of electrolyte-free solutions alone should be avoided because of the risk of over-hydration. In these cases, furosemide should be administered and the volume of urine excreted hourly should be replaced with 5 % glucose solution (alternatively, haemodialysis or haemoperfusion should be considered).

5.4.2.2. *Further endocrine substitution*

The benefit of additional exogenous hormonal supplementation continues to be controversial because of conflicting evidence. Until confirmative results are available, hormone-replacement therapy should be reserved for unstable patients despite optimal haemodynamic care [2-3, 23].

Especially in haemodynamically unstable donors, methylprednisolone should be administered immediately after BD causing septic shock-like symptoms, given the anticipated up-regulation of pro-inflammatory cytokines due to its ability to increase production of endogenous epinephrine, and the positive impact on lungs and liver transplant functioning. The use of methylprednisolone (bolus 15 mg/kg) at the time of BD is commonly recommended for haemodynamic and lung-protective effects and has been shown to improve donor oxygenation and lung utilisation, although further research is needed to assess the effect of steroids in lung donors [24].

Alternatively, early substitutive administration of hydrocortisone can be performed (100 mg bolus initially, 200 mg/day continuous administration) [24-27]. Early substitutive administration of glucocorticoids in a potential DBD donor with circulatory failure allows significant reduction of the cumulative amount and duration of vasopressor therapy. In cases of steroid supplementation, glucose dysregulation must be corrected by insulin administration (target blood glucose < 150 mg/dL (< 8.3 mmol/L)) to exclude polyuria due to glucosuria. Insulin infusion may provide benefits of anti-inflammation and reduced cytokines in addition to the benefits of good glycaemic control.

Retrospective studies have shown improved organ donation rates and transplant outcomes with donor steroid treatment, though there is no evidence from randomised clinical trials (RCTs) across heart, lung, liver and kidney transplantation that donor treatment with steroids improves organ donation/transplant rates or transplant outcomes. (See Appendix 7.)

The lack of large prospective randomised studies about the benefit of routine administration of tri-iodothyronine (T_3) precludes recommendation of this option. However, it may be useful in unstable potential donors unresponsive to volume loading and restoration of vascular tone as a rescue therapy combined with vasopressin and methylprednisolone [28].

Many retrospective studies demonstrate improved organ procurement rates from donors treated with thyroid hormones, but this benefit has not been confirmed by a randomised controlled trial. (See Appendix 7.)

5.4.3. Persistent arterial hypotension and use of vasopressors

A target mean arterial pressure of 60–75 mmHg should be achieved in adults, with diuresis of 0.5–1.5 mL/kg/h. This can be achieved by:

a. discontinuation of all medications with hypotensive effects or side-effects,
b. replacing volume deficits with crystalloid/colloid solutions up to a CVP 4-12 mmHg (4-8 mmHg in potential lung donors).

If adequate mean arterial pressure cannot be achieved by fluid replacement, then vasopressors are indicated.

5.4.3.1. *Vasopressors*

Despite fluid replacement, administration of vasopressors frequently becomes necessary. However, most donor co-ordinators and critical care physicians rely on the measurement of CVP as an indirect indicator of fluid status [29, 30]. Nevertheless, extended haemodynamic monitoring (e.g. echocardiography, minimally invasive cardiac output measurements or pulmonary artery catheter) should be highly recommended in donors with persistent hypotension. This will facilitate determination of the precise haemodynamic profile and causes of hypotension (see Figure 5.2) [31-33]. The use of extended haemodynamic monitoring and other parameters, such as extravascular lung water, has been recently proposed to improve the number of lungs available for transplantation [14, 34].

a. Norepinephrine is often the first choice vasopressor in these cases and should be administered until the target mean arterial pressure is reached. An ongoing dose exceeding 0.2 µg/kg/min should raise serious concerns about the possible complications mentioned below.
b. Myocardial dysfunction can be assessed and quantified by echocardiography. In such cases, administration of an inotropic drug, such as dobutamine in association with norepinephrine, is recommended.
c. Vasopressin (1 IU as bolus, 0.5-4 IU/h as a recommended dose) is still under evaluation for its use in DBD donors as a way to gradually reduce vasopressor administration, while maintaining target parameters after appropriate correction of all other issues to decrease vasopressor dosages. Given vasopressin's lack of cardiotoxicity and as a result of normalisation of systemic vascular resistance, cardiac function can be improved. As a result, in a study, the number of transplantable hearts

(most of which had initially been evaluated as unsuitable for transplantation) rose by 35 % [31-32].

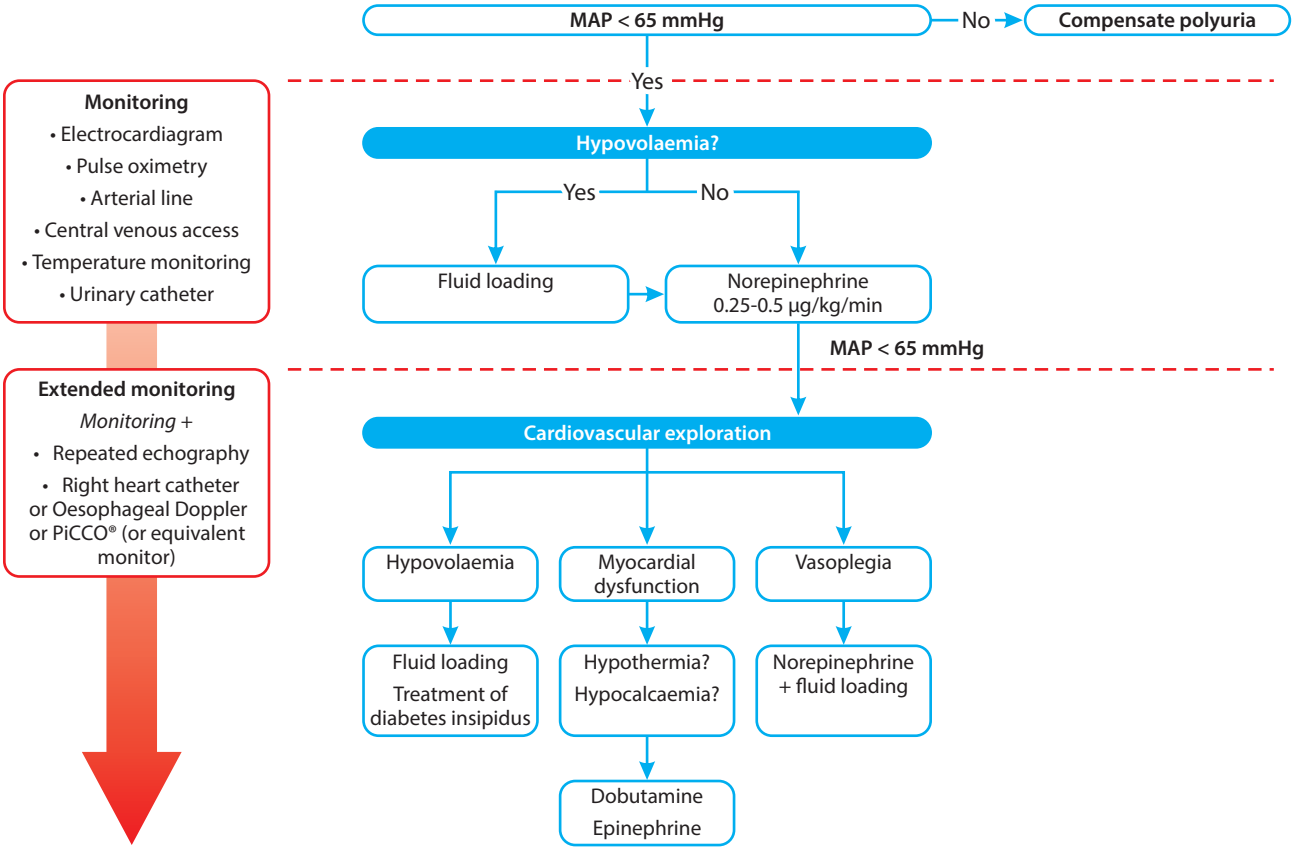
d. An ongoing dose exceeding 0.5 µg/kg/min should raise serious concerns about the possible complications mentioned below. The pre-treatment of donors with low doses of dopamine (< 4 µg/kg/min) has been shown to reduce the need for dialysis after kidney transplantation without a significant clinical impact on graft or patient survival as well as to mitigate cold preservation injury to cardiomyocytes in heart grafts [33, 35]. Since dopamine directly interacts with the cellular membrane and is capable of protecting endothelial cells from oxidative stress during cold storage, the application of low-dose dopamine is intended to protect kidney grafts from damage related to prolonged ischaemia time exclusively (and not as vasopressor). This was confirmed by the randomised trial conducted by Schnülle *et al.* in the sub-cohort of grafts exposed to long ischaemia times, by reducing the rate of delayed graft function [35]. On the contrary, high doses of dopamine (> 10 µg/kg/min) must be avoided because, due to its action on α-adrenergic receptors, it can induce a progressive renal and systemic vasoconstriction, as well as the depletion of endogenous norepinephrine and of ATP (adenosine triphosphate) reserves in the organs, and it can affect their function after transplantation, especially in the case of the heart.

Whenever the administration of catecholamines is guided by direct cardiac output measurement (minimal dose to maintain an ideal cardiac output and systemic vascular resistance), donor co-ordinators and ICU physicians should not be worried about dose requirements.

5.4.3.2. *Ventilation, infusion and pumping*

The Ventilation, Infusion and Pumping/Pressure (VIP) approach (Figure 5.3) is a simple mnemonic originally proposed to bring together key aspects of the management of shock states [36]. An adapted version of the VIP approach was proposed providing a systematic sequence of procedures aimed at restoring oxygen delivery (DO_2) by adjusting mechanical ventilation, fluid and drug infusions, and maintaining heart function (pumping/pressure).

Figure 5.2. **Haemodynamic objectives and care in the management of the potential donor after brain death**



MAP = mean arterial pressure.

Source: Charpentier J, Cariou A. Objectifs et moyens de la prise en charge hémo-dynamique [33].

A bedside checklist based on the adapted VIP approach was implemented as a quality improvement intervention in 27 hospitals over 24 months. The adherence to the goal checklist was associated with a reduction of the odds of cardiac arrest episodes (the number of cardiac arrest episodes was inversely proportional to the number of treatment goals met), an increase in actual donors and in the number of organs procured per donor [36]. An adequate understanding of BD pathophysiology and related organ damage is needed in order to tailor the treatment of circulatory instability and to optimise the timing of organ procurement. The 'relax and repair' approach and an active 'wait, treat and see' have been suggested to increase the number and quality of kidney and heart transplants [36].

5.4.3.3. *Cardiac arrest*

The management of episodes of cardiac arrest in potential organ donors should be based on the European Resuscitation Council guidelines [37-38]. Cardiac arrest should not occur, particularly when other therapeutic options are available (e.g. ECMO), hence this is an exceptional complication.

5.4.4. Hypokalaemia/hypernatraemia

Hypokalaemia can be corrected by replacing potassium. Normalisation of elevated serum sodium levels may be difficult. When hypernatraemia exists in combination with volume deficiency – CVP < 7 mmHg (see §5.4.2.1) – water, through a nasogastric tube, and 5 % glucose solution (together with insulin) may be administered as an infusion (after isotonic sodium chloride to restore intravascular volume). Blood glucose and potassium levels should also be monitored. As there is a sharp decline in the metabolic rate of donors, administration of large volumes of 5 % glucose solution may lead to severe hyperglycaemia, with consequent osmotic diuresis, if not properly monitored. In the case of hypernatraemia with adequate blood volume or hypervolaemia (CVP > 10 mmHg), administration of electrolyte-free solutions alone will cause over-hydration. In such cases, furosemide should be administered and the volume of urine excreted hourly should be replaced with 5 % glucose solution. Administration of clear water through the nasogastric tube may help to achieve normonatraemia.

5.4.5. Hypothermia and dysregulation of body temperature

A minimum body temperature of 35 °C-37 °C should be maintained in DBD donors. This can be achieved by:

a. reducing passive heat loss by covering the donor with, for example, metal foil, using electric blankets and hot-air blowers,
b. heat-infusion solutions in water baths or special infusion heaters.

Untreated and/or uncontrolled hypothermia (< 35 °C) causes numerous complications that impair the transplant success of organs, such as:

a. In general it is seen that metabolic activity, energy and oxygen consumption of the organs fall at lower body temperatures. This causes adaptive impairment of organ function (heart, liver and/or kidneys), which may have a negative impact on organ-related functional diagnoses. At the same time, hyperglycaemia may increase as insulin production and insulin efficacy are reduced and the rate of glucose metabolism decreases.
b. Cardiac contractility declines and the risk of arrhythmia increases, both resulting in under-perfusion of the organs.
c. Erythrocyte flexibility declines, causing disruption to micro-circulation in the organs and reducing oxygen release into the tissues.
d. Hypothermia enhances coagulation disorders.

In some cases, hyperthermia (> 38 °C) may occur because of failure of central temperature regulation and SIRS without infection, or because of SIRS combined with a relevant infection (in which case the cause should be sought and proper treatment should be initiated).

There is extremely limited clinical evidence for the use of therapeutic hypothermia for donors following brain death, but there is one RCT in renal transplantation that does show a significant reduction in DGF [12]. The same effect on reducing DGF is supported by one large cohort study. (See Appendix 9.)

5.4.6. Spinal vegetative dysregulation and movements

The typical indicative parameters are hypertension, tachycardia and massive reflex movements.

5.4.7. Lung-protective treatment and ventilation

Lung grafts are procured in only 15-20 % of all multi-organ donors. Lungs are susceptible to damage by a number of factors, e.g. resuscitation manoeuvres, neurogenic oedema, pneumonia and aspiration of gastric content, SIRS (occurring before, during and after BD) and suboptimal mechanical ventilation. Alveolar recruitment measures should always be carried out regularly in all potential donors, not only for reversing pulmonary deterioration, but also as a preventive management measure in cases with PaO_2/FiO_2 higher than 300 mmHg (40.0 kPa) or a normal chest X-ray.

Nowadays a lung-protective strategy [13, 39] in donor ventilation is recommended, which is equivalent to standard patient care, with the goal of increasing the number of lungs eligible for transplantation. It has been shown that lung-protective protocols of this kind are easily applied in all types of centre, without requiring any specific training [14], and may therefore help to relieve the shortage of lungs for transplantation. A lung-protective strategy is based on:

a. protective ventilation with low tidal volume, ventilator recruitment manoeuvres, high PEEP value, fluid restriction with reduced target extravascular lung water values (see Table 5.3),
b. invasive haemodynamic monitoring to optimise haemodynamic parameters,
c. use of steroids.

This strategy includes methods to prevent atelectasis and infection through these precautions:

- continuous mucolysis,
- humidification of respiratory gases,
- aspiration of secretions,
- changes of body position and head-of-bed elevation (if no contraindications),
- disinfection of the hands preceding measures on the respiratory tract,
- oral care and oral decontamination,
- avoidance of oral aspiration (e.g., by using cuff pressure measuring and subglottic secretion drainage).

The targeted parameters, particularly if lung procurement is planned, are:

a. $PaCO_2$ of 35–40 mmHg (4.6–5.3 kPa),
b. PaO_2 of 80–100 mmHg (10.6–13.3 kPa),
c. PEEP ≥ 5 cm H_2O, even in cases of adequate oxygenation levels,
d. pH of 7.3–7.5.

Table 5.4. **Interventions for a lung-protective strategy**

Intervention	Comment/Recommendation
Apnoea test	It should be performed with ventilator on CPAP mode. It is recommended to perform a single recruitment manoeuvre immediately after testing with attention to haemodynamic instability
Mechanical ventilation	Lowest FiO_2 possible Plateau pressure < 30 cm H_2O PEEP 8-10 cm H_2O (a high PEEP prevents lung oedema and helps prevent atelectasis)* Tidal volume 6-8 mL/kg
Recruitment manoeuvres**	Once per hour and after every disconnection from the ventilator
Bronchoscopy	With bilateral bronchoalveolar lavage, immediately after brain death
Close monitoring of haemodynamics [25-26]	With PiCCO or equivalent monitor EVLW < 10 mL/kg (administering diuretics, if necessary) CVP < 8 mmHg
Methylprednisolone	15 mg/kg after brain death declaration
Semi-lateral decubitus position	In lung donors with PaO_2/FiO_2 <300 mmHg
Closed circuit for tracheal suction	Any loss of pressurisation caused by tube disconnection must be avoided to decrease the risk of atelectasis
Avoid any decrease in oxygenation	Appropriate ventilation should be ensured during stay at ICU, during any transfer within the hospital and during surgery in the operating theatre at procurement with a target PaO_2/FiO_2 > 300 mmHg (> 40.0 kPa)

Note: CPAP: continuous positive airway pressure. CVP: central venous pressure. EVLW: extravascular lung water. FiO_2: fraction of inspired oxygen. ICU: intensive care unit. PEEP: positive end-expiratory pressure.

* Optimal ventilator settings in a protective mechanical ventilation include lowering the driving pressure (ΔP=plateau pressure minus PEEP), appropriate target being probably < 14 cm H_2O [40] or a bit higher < 19 [41-43].

** Suggested technique: controlled ventilation (plateau pressure limit of 35 mm Hg) with PEEP of 18-20 cm H_2O for 1 minute, and decreased 2 cm H_2O each minute; after that we increased 50 % tidal volumes for 10 breaths [14, 15, 35, 39].

Uncorrected hypocapnia in a donor, due to prior hyperventilation to lower cerebral blood volume and intracranial pressure, causes severe respiratory alkalosis. This has an impact on circulation and the oxygen-binding (oxygen-dissociation) curve because of reduced metabolism of the donor after brain death.

A lung-protective strategy aimed at improving lung function and protection in order to enable lung donation is summarised in Table 5.4 [13, 14, 34, 39].

5.4.8. Nutritional support

Patients admitted to critical care units are usually submitted to enteral nutrition as early as possible, either exclusively or combined with parenteral nutrition, providing no contraindications to enteral nutrition exist. This nutrition strategy prevents bacterial translocation through gut mucosa, which can lead to further infectious complications. The DBD donor has no vagal stimulation of the gastrointestinal tract, thus an impaired gastric and enteral motility, which may lead to limited tolerance of high-volume enteral feeding. Worldwide, there is no uniform policy on donor feeding or fasting.

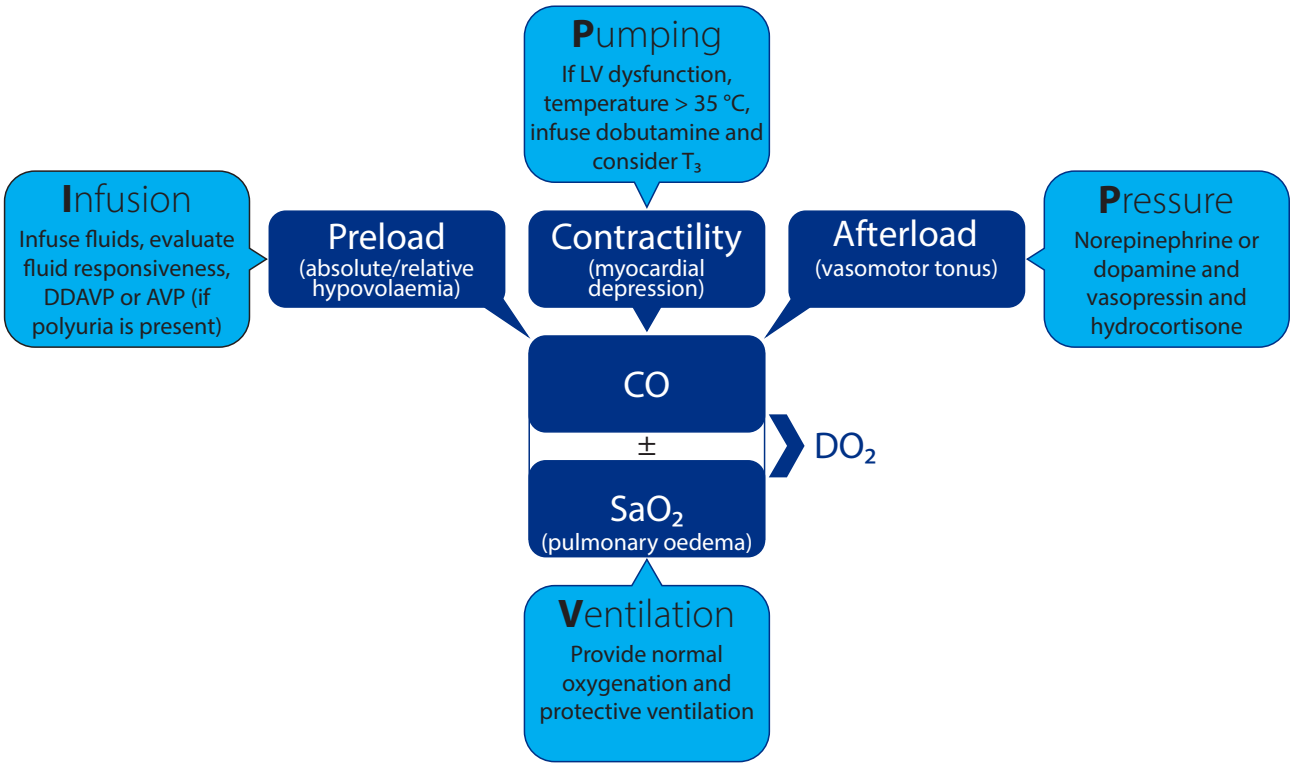
The Consensus statement of the Society of Critical Care Medicine and others on the management of potential donors recommends that, in the absence of contraindications, enteral feeding of the donor should be continued, because it is suggested that hepatic glycogen reserves may provide nutrients during cold ischaemia time, thus improving liver graft function [44]. One randomised open-label trial of DBD donors found no difference in all-cause recipient mortality at 6 months regardless of feeding status of the donors, but it showed increased resting energy expenditures in donors who received corticosteroids as a part of donor management [45]. Further investigations are needed in this area, with the aim to define the best strategy of enteral nutrition regarding type and volume of nutrition, especially in DBD donors receiving corticosteroid therapy.

Special consideration of enteral nutrition should be taken into account in intestinal donors. Animal models have demonstrated gut mucosa and villus height decline within 12 hours of the fasting state before organ procurement, compared to fed animals [46]. Although this has not been tested in humans, it seems reasonable to consider continuation of enteral feeding in potential intestinal donors. If the enteral approach is contraindicated, sterile fluid should be administered through the gastric tube [47].

5.4.9. Haemostasis during organ retrieval

Abnormalities in haemostasis, which frequently occur in DBD donors, are linked to the destruction of

Figure 5.3. **Pathophysiology of haemodynamic instability after brain death and the adapted ventilation, infusion and pump/pressure (VIP) approach for clinical maintenance of potential brain-dead donors**



AVP: arginine vasopressin. CO: cardiac output. DDAVP: Desmopressin AVP. DO_2: oxygen delivery. LV: Left valve. SaO_2: oxygen saturation.

cerebral tissues (by disseminated intravascular coagulation, fibrinolysis).

Platelets and haemostatic factors should be monitored and maintained until the end of the procurement procedure, at the following levels:

a. platelets > 50 G/L,
b. fibrinogen > 1 g/L (> 100 mg/dL),
c. prothrombin time > 40 % and/or TCA ratio < 1.5.

Transfusion of erythrocyte concentrates should also be planned to maintain oxygen transport capacity. The critical haematocrit for DBD donors depends on age and previous medical history. International guidelines and other sources recommend taking surrogate parameters (central venous saturation > 70 %, normal range for serum lactic acid concentration) as a basis. Haematocrit levels of over 20 % should be targeted in cases where circulation is stable, and over 30 % in cases of circulatory instability (transfusion of packed red blood cells in DBD donors is associated with a lower rate of delayed graft renal function [48]). However, these transfusional targets have to be considered with precaution as it is possible that haemodilution increases the risk of false negative results in serology of donors; other risks are inflammatory activation related to the time of the blood collection (either for red blood cells or fresh frozen plasma), donor's lung injury and transmission of virus diseases to organ recipients [49].

Cytomegalovirus (CMV) transmission is prevented by transfusion of leukocyte-depleted blood products (particularly erythrocytes and platelets concentrates), a treatment which is consistent with the fact that CMV is a leukocyte-associated pathogen. CMV is a major concern when it comes to transfusing organ donors or immunocompromised organ recipients. For this reason, organ recipients, but also organ donors, are given CMV-seronegative or leukocyte-depleted blood products, even where this risk is generally considered negligible; however, this is still not the usual transfusion practice in many countries and hospitals throughout Europe [50]. The residual risk of transfusion-transmitted CMV infection can be significantly reduced by use of leukocyte-depleted blood components [51].

5.4.10. Multi-organ management of donation after brain death

Multi-organ DBD management should be approached as a global strategy requiring careful bedside management to avoid losing donors due to inadequate protocols. Implementing an intensive donor-treatment protocol that considers the DBD donor as a critical patient is cheap, available in all critical care units all over the world and increases the organ procurement rate [52].

Some principles of donor management are generally applicable, whereas others are targeted to a specific organ. Competing requirements for organ perfusion may call for antagonistic strategies, such as fluid replacement or high PEEP. A restrictive fluid balance is associated with higher rates of lung procurement, whereas aggressive volume repletion facilitates the maintenance of kidney function. Moreover, consistently high PEEP (> 10 cm H_2O) or alveolar recruitment manoeuvres with PEEP over 16-20 cm H_2O may limit the formation of lung oedema and prevent atelectasis, but might produce a haemodynamic instability in unmonitored organ donors.

However, a strict and intensive lung-donor-treatment protocol based on protective mechanical ventilation, advance cardiac monitoring and hormonal therapy does not affect either the number of other grafts procured (heart, liver, pancreas and kidneys) nor the rates of graft and patient survival. Moreover, in grafts as sensitive to restrictive fluid balance as the kidney or the heart, no negative effect has been observed in rates of graft procurement or recipient outcomes due to inadequate perfusion of vital organs with this bedside treatment [20].

5.4.11. Optimising the timing to perform organ procurement

Some authors have proposed increasing the time from BD until organ procurement to more than 20 hours, because longer treatment times have been associated with enhanced gas exchange, reduced lung water, inotropic weaning and improved lung and heart transplantation rates [53-54]; this option to delay organ procurement has been included in several national guidelines, e.g. Canada [55], Ireland [56]. Prolonged management of the DBD donor is not necessarily associated with a reduction in the number of organs procured. However, it has not been demonstrated that time is the factor that improves grafts after brain death, rather than appropriate and early treatment by skilled personnel immediately after BD declaration.

This approach is very complicated to implement because of the logistical complexity of multi-organ donation and the risk of cardiac arrest or deterioration of other organs [57].

There is no minimum time range. However, left ventricular systolic dysfunction detected by echocardiography in the absence of a history of

heart disease is the single most common cause for non-transplantation of hearts. The phenomenon of ventricular cardiac dysfunction in the donor, just after the diagnosis of BD, may be transient [58-60] and, with proper treatment, hearts could be procured to transplantable status [61]. Therefore, advanced cardiovascular monitoring, with serial echocardiograms – preferably trans-oesophageal rather than transthoracic – separated by several hours and until weaning of cathecholamines, should be performed to monitor the response to medical management when early cardiac dysfunction is identified in potential donors.

5.4.12. Donor management during organ procurement

Multi-organ procurement [62] is an extensive procedure with wide exposure of surgical field, including incision from suprasternal notch to pubis. It may be up to 3-4 hours long. Proper anaesthetic treatment during this period may help to avoid organ damage prior to that explantation.

Donor monitoring during organ procurement should be similar to the monitoring previously performed in the critical care unit (see Appendix 5, Appendix 6). Central venous line should be preserved for CVP monitoring and delivery of vasoactive drugs. Large-diameter venous catheters for rapid infusion might be useful in case of sudden unexpected bleeding from damaged large vessels. Active warming of the organ donor should be considered in advance if prolonged procedures including liver and pancreas procurement are planned. This may prevent hypothermia and subsequent circulatory disturbances.

Ventilation should be similar in the operating room to the ventilation in the critical care unit, with FiO_2 not exceeding 40 % if procurement of lungs is anticipated. Although patients in BD do not have pain perception, spinal somatic and sympathetic reflexes may appear. Therefore, long-acting non-depolarising muscle relaxants should be used to facilitate surgical exposure. Hypertension and tachycardia should be controlled with volatile anaesthetics and opioids. Severe bradycardia, if it appears, is resistant to atropine and should be treated with a directly acting chronotrope such as isoproterenol, or even by intravenous pacing. Dextrose-containing solutions should be avoided at this stage because they may aggravate already existing hyperglycaemia and be the cause of osmotic diuresis and electrolyte disturbances.

An anaesthesiologist may be asked by surgical teams to collect blood samples for several laboratory tests and for administration of heparin, phentolamine or any other medication according to current protocols. In the case of heart and/or lung procurement, central venous catheters and pulmonary catheter have to be withdrawn prior to aorta cross-clamping. After cross-clamping, all supportive treatment should be terminated and the ventilator should be switched off, with the exception of cases of lung procurement, when manual ventilation should be maintained according to the procurement team's suggestions.

5.5. Conclusion

To conclude, BD induces a plethora of deleterious events leading to rapid deterioration of organ function. Optimal management of the DBD donor during this period remains critical to the successful outcome of transplantation. The impact of meeting donor-management goals [8], defined as normal cardiovascular, pulmonary, renal and endocrine endpoints, is associated with an increase in both the quantity and quality of grafts. Implementation of donor-management goal protocols to improve outcomes is highly recommended. Once the donor-management goals are achieved and well maintained, the optimal timing for organ procurement is still a question for debate along with consideration of, for example, 'spontaneous' heart recovery with time [60].

Progress in organ transplantation technologies and the development of *ex situ* organ perfusion systems, which mimic physiological conditions and allow prolonged preservation and better graft survival rates, are very promising and can be actively incorporated into *ex situ* pre-transplant reconditioning of donor organs.

With time and more successful interventions, it may be possible to further address the ongoing shortage of donor organs. Understanding the molecular inflammatory responses and utilising interventions that can reduce haemodynamic instability, inflammation and SIRS are the keys to further advancing donor management.

To achieve treatment goals requires high-quality intensive care, specific education, proper experience and commitment, as well as time for treatment. Adherence to guidelines should be systematically audited in critical care units. Quality indicators and quality assessment should be used.

Research agenda

From the literature and discussion of the available evidence, several topics have been identified for which evidence is inconsistent, insufficient or non-existent. The authors of this guide recommend that future research, where possible in well-designed

randomised clinical trials, should focus on the following research gaps:

1 Use of steroids in the management of deceased donors.
2 Use of thyroid hormones in the management of deceased donors.
3 Use of therapeutic hypothermia in the management of deceased donors, particularly in non-renal organs.

5.6. References

1. DuBose J, Salim A. Aggressive organ donor management protocol. *J Intensive Care Med* 2008;23:367-75.
2. Wood KE, Becker BN, McCartney JG *et al.* Care of the potential donor. *N Engl J Med* 2004;351:2730-39.
3. Kutsogiannis DJ, Pagliarello G, Doig C *et al.* Medical management to optimize donor organ potential: review of the literature. *Can J Anaesth* 2006;53:820-30.
4. Bugge JF. Brain death and its implications for management of the potential organ donor. *Acta Anaesthesiol Scand* 2009;53:1239-50.
5. Mascia L, Mastromauro I, Viberti S *et al.* Management to optimize organ procurement in brain-dead donors. *Minerva Anestesiol* 2009;75:125-33.
6. McKeown DW, Bonser RS, Kellum JA. Management of the heartbeating brain-dead organ donor. *British J Anaesthesia* 2012;108(S1):i96-i107.
7. Patel MS, Zatarain J, De La Cruz S *et al.* The impact of meeting donor management goals on the number of organs transplanted per expanded criteria donor. A prospective study from the UNOS Region 5, Donor Management Goals Workgroup. *JAMA Surg* 2014;149: 969-75.
8. Hensley FA, Martin DE, Gravlee GP. *A practical approach to cardiac anesthesia*. 5th edition, paperback, Philadelphia: Lippincott Williams & Wilkins (23 Oct 2012).
9. Patel MS, Mohebali J, Sally M *et al.* Deceased organ donor management: does hospital volume matter? *J Am Coll Surg* 2017;224(3):294-300.
10. Watts PR, Thom O, Fraser J. Inflammatory signalling associated with brain-dead organ donation: from brain injury to brain stem death and posttransplant ischaemia reperfusion injury. *J Transpl* 2013; https://doi.org/10.1155/521369.
11. Marsolais P, Durand P, Charbonney E *et al.* The first 2 years of activity of a specialized organ procurement center: report of an innovative approach to improve organ donation. *Am J Transplant* (2016) Nov 22. https://doi.org/10.1111/ajt.14139 [epub ahead of print]. PubMed: 27873446.
12. Niemann CU, Feiner J, Swain S *et al.* Therapeutic hypothermia in deceased organ donors and kidney-graft function. *N Engl J Med* 2015;373(5);405-14.
13. Miñambres E, Coll E, Duerto J *et al.* Effect of an intensive lung donor management protocol on lung transplantation outcomes. *J Heart Lung Transplant* 2014;33:178-84.
14. Miñambres E, Pérez-Villares JM, Chico M *et al.* Lung donor treatment protocol in brain dead-donors: a multicenter study. *J Heart Lung Transplant* 2015;34: 773-80.
15. Cittanova ML, Leblanc I, Legendre C *et al.* Effect of hydroxyethylstarch in brain-dead kidney donors on renal function in kidney-transplant recipients. *Lancet* 1996;348:1620-2.
16. Brunkhorst FM, Engel C, Bloos F *et al.* Intensive insulin therapy and pentastarch resuscitation in severe sepsis. *N Eng J Med* 2008;358:125-39.
17. Blasco V, Leone M, Antonini F *et al.* Comparison of the novel hydroxyethylstarch 130/0.4 and hydroxyethylstarch 200/0.6 in braindead donor resuscitation on renal function after transplantation. *Br J Anaesth* 2008;100:504-8.
18. Reinhart K, Perner A, Sprung CL *et al.* Consensus statement of the ESICM task force on colloid volume therapy in critically ill patients. *Intensive Care Med* 2012;38:368-83.
19. Kotloff RM, Blosser S, Fulda GJ *et al.* Management of the potential organ donor in the ICU: Society of Critical Care Medicine/American College of Chest Physicians/Association of Organ Procurement Organizations Consensus Statement. *Crit Care Med* 2015; 43:1291-325.
20. Miñambres E, Pérez-Villares JM, Terceros-Almanza L *et al.* An intensive lung donor treatment protocol does not have negative influence on other grafts: a multicentre study. *Eur J Cardiothorac Surg.* 2016 June;49(6): 1719-24.
21. Cheisson G, Duranteau J. Modalités de la prise en charge hémodynamique. In: G Boulard, P Guiot, T Pottecher, A Tenaillon, eds. *Prise en charge des sujets en état de mort encéphalique dans l'optique du prélèvement d'organes et de tissus*. Paris: Elsevier, 2005;135-48.
22. Benck U, Gottmann U, Hoeger S *et al.* Donor desmopressin is associated with superior graft survival after kidney transplantation. *Transplantation* 2011;92: 1252-8.
23. Venkateswaran RV, Steeds RP, Quinn DW *et al.* The haemodynamic effects of adjunctive hormone therapy in potential heart donors: a prospective randomized double-blind factorially designed controlled trial. *Eur Heart J* 2009;30:1771-80.
24. Follette DM, Rudich SM, Babcock WD. Improved oxygenation and increased lung donor recovery with high-dose steroid administration after brain death. *J Heart Lung Transplant* 1998;17:423-9.
25. Kotsch K, Ulrich F, Reutzel-Selke A *et al.* Methylprednisolone therapy in deceased donors reduces

inflammation in the donor liver and improves outcome after liver transplantation: a prospective randomized controlled trial. *Ann Surg* 2008;248: 1042-50.

26. Pinsard M, Ragot S, Mertes JM *et al.* Interest of low-dose hydrocortisone therapy during brain-dead organ donor resuscitation: the CORTICOME study. *Crit Care* 2014;18:R158.
27. Dupuis S, Amiel JA, Desgroseilliers M *et al.* Corticosteroids in the management of brain-dead potential organ donors: a systematic review. *Br J Anaesth* 2014; 113:346-59.
28. Novitzky D, Mi Z, Sun Q *et al.* Thyroid hormone in the management of 63,593 brain-dead organ donors: a retrospective analysis. *Transplantation* 2014;98:1119-27.
29. Pennefather SH, Bullock RE, Dark JH. The effect of fluid therapy on alveolar arterial oxygen gradient in brain-dead organ donors. *Transplantation* 1993;56: 1418-22.
30. Vincent JL, Rhodes A, Perel A *et al.* Clinical review: update on hemodynamic monitoring – a consensus of 16. *Crit Care* 2011;15(4):229.
31. Pennefather SH, Bullock RE, Mantle D *et al.* Use of low dose arginine vasopressin to support brain-dead organ donors. *Transplantation* 1995;59:58-62.
32. Rosendale JD, Kaufmann HM, McBride M *et al.* Aggressive pharmacologic donor management results in more transplanted organs. *Transplantation* 2003;75: 482-7.
33. Charpentier J, Cariou A. Objectifs et moyens de la prise en charge hémo-dynamique. In: G Boulard, P Guiot, T Pottecher, A Tenaillon, eds. *Prise en charge des sujets en état de mort encéphalique dans l'optique du prélèvement d'organes et de tissus*. Paris: Elsevier, 2005:125-35.
34. Venkateswaran RV, Dronavalli V, Patchell V *et al.* Measurement of extravascular lung water following human brain death; implications for lung donor assessment and transplantation. *Eur J Cardiothorac Surg* 2013;43:1227-32.
35. Schnülle P, Gottmann U, Hoeger S *et al.* Effects of donor pretreatment with dopamine on graft function after kidney transplantation: a randomized controlled trial. *JAMA* 2009;302:1067-75.
36. Martin-Loeches I, Sandiumenge A, Charpentier J *et al.* Management of donation after brain death (DBD) in the ICU: the potential donor is identified, what's next? *Intensive Care Med* 2019;45:322-30.
37. Merchant, RM, Topjian AA, Panchal AR *et al.* (2020). Part 1: Executive Summary: 2020 American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. *Circulation* 2020;142(16_suppl_2): S337-S357. https://doi.org/10.1161/CIR.0000000000000918.
38. Perkins GD, Graesner J-T, Semeraro F *et al.* (2021). European Resuscitation Council Guidelines 2021: Executive summary. *Resuscitation* 161: 1-60.
39. Mascia L, Pasero D, Slutsky A *et al.* Effect of a lung-protective strategy for organ donors on eligibility and availability of lungs for transplantation: a randomized controlled trial. *JAMA* 2010;304(23):2620-7.
40. Amato MB, Meade MO, Slutsky AS *et al.* Driving pressure and survival in the acute respiratory distress syndrome. *N Engl J Med*. 2015 Feb 19;372(8):747-55.
41. Bagchi A, Rudolph MI, Ng PY *et al.* The association of postoperative pulmonary complications in 109,360 patients with pressure-controlled or volume-controlled ventilation. *Anaesthesia* 2017 Sep 11. https://doi.org/10.1111/anae.14039.
42. Villar J, Martín-Rodríguez C, Domínguez-Berrot AM *et al.* Spanish Initiative for Epidemiology, Stratification and Therapies for ARDS (SIESTA) Investigators Network. A quantile analysis of plateau and driving pressures: effects on mortality in patients with acute respiratory distress syndrome receiving lung-protective ventilation. *Crit Care Med* 2017 May;45(5):843-50.
43. Raymondos K, Dirks T, Quintel M *et al.* Outcome of acute respiratory distress syndrome in university and non-university hospitals in Germany. *Crit Care* 2017 May 30;21(1):122.
44. Kotlo RM, Blosser S, Fulda GJ *et al.* Management of the potential organ donor in the ICU: Society of Critical Care Medicine/American College of Chest Physicians/Association of Organ Procurement Organizations consensus statement. *Crit Care Med* 2015;43(6):1291-1325. https://doi.org/10.1097/CCM.0000000000000958.
45. Hergenroeder GW, Ward NH, Yu X *et al.* Randomized trial to evaluate nutritional status and absorption of enteral feeding after brain death. *Prog Transplant* 2013;23(4):374-82.
46. Salehi P, Churchill TA. The influence of short-term fasting on quality of small bowel graft preservation. *Cryobiology* 2005;50:83-92.
47. Fischer-Fröhlich CL, Konigsrainer A, Schaffer R *et al.* Organ donation: when should we consider intestinal donation. *Transpl Int* 2012;25:1229-40.
48. de la Cruz JS, Sally MB, Zatarain JR *et al.* The impact of blood transfusion in deceased organ donors on the outcome of 1884 renal grafts from United Network for Organ Sharing Region 5. *J Trauma Acute Care Surg* 2015;79(4 Suppl 2):S164-70.
49. Iwamoto M, Jernigan DB, Guasch A *et al.* Transmission of West Nile virus from an organ donor to four transplant recipients. *N Engl J Med* 2003;348(22): 2196-203.
50. EDQM: *The collection, testing and use of blood and blood components in Europe* (report of 2014). Strasbourg: EDQM, available at www.edqm.eu/en/

blood-transfusion-reports-70.html, accessed 8 May 2021.

51. Torre-Cisneros J, Aquado JM, Caston JJ *et al.* Management of cytomegalovirus infection in solid organ transplant recipients: SET/GESITRA-SEIMC/REIPI recommendations, *Transplant Rev (Orlando)*, 2016; 30(3):119-43, available at www.ncbi.nlm.nih.gov/pubmed/27132815, accessed 8 May 2021.
52. Singbartl K, Murugan R, Kaynar A *et al.* Intensivist-led management of brain-dead donors is associated with an increase in organ recovery for transplantation. *Am J Transplant* 2011;11:1-5.
53. Inaba K, Branco BC, Lam L *et al.* Organ donation and time to procurement: late is not too late. *J Trauma* 2010;68:1362-6.
54. Christmas AB, Bogart TA, Etson KE *et al.* The reward is worth the wait: a prospective analysis of 100 consecutive organ donors. *Am Surg* 2012;78:296-9.
55. Shemie SD, Ross H, Pagliarello J *et al.* Organ donor management in Canada: recommendations of the forum on Medical Management to Optimize Donor Organ Potential. *CMAJ* 2006;March 14;174(6):S13-S30.
56. Dwyer R, Motherway C, Phelan D. *Diagnosis of brain death in adults: guidelines*. Dublin: Intensive Care Society of Ireland, 2010, available at www.anaesthesia.ie/attachments/article/92/ICSI%20Guidelines%20MAY10.pdf, accessed 8 May 2021.
57. Domínguez-Gil B, Miñambres E, Matesanz R. Contemporary organizational aspects of heart transplantation: the procurement perspective. *Rev Esp Cardiol* 2015;15(B):13-20.
58. Zaroff JG, Babcock WD, Shiboski SC *et al.* Temporal changes in left ventricular systolic function in heart donors: results of serial echocardiography. *J Heart Lung Transplant* 2003;22:383-8.
59. Casartelli M, Bombardini T, Simion D *et al.* Wait, treat and see: echocardiographic monitoring of brain-dead potential donors with stunned heart. *Cardiovasc Ultrasound* 2012;Jun 21;10:25.
60. Borbely XI, Krishnamoorthy V, Modi S *et al.* Temporal changes in left ventricular systolic function and use of echocardiography in adult heart donors. *Neurocrit Care* 2015;23:66-71.
61. Simion D, Casartelli ML, Procaccio F. Early targeted treatment may facilitate complete weaning from vasopressors and recovery of stunned hearts in unstable potential organ donors: a new golden time concept. *Organs, Tissues & Cells* 2014;17:49-52.
62. Busque S, Melcher M, Desai D *et al.* Multiorgan procurement. In: Jaffe RR, Samuels S, eds. *Anesthesiologist's manual of surgical procedures*. Philadelphia and London: Wolters Kluwer/Lippincott Williams & Wilkins, 2009.

Related material

Appendix 5. Procurement surgery in brain-death donors: tasks for the anaesthesiologist
Appendix 6. Checklist for the anaesthesiologist in the operating room
Appendix 7. The use of steroids in the management of deceased donors
Appendix 8. The use of thyroid hormones in the management of deceased donors
Appendix 9. The use of therapeutic hypothermia in the management of deceased donors

Chapter 6. General donor characterisation, assessment and selection criteria

6.1. Introduction

In order to minimise the risks of transplantation and to improve the whole process, from donor suitability assessment via allocation to individualised risk–benefit assessment in a final donor–recipient match, it is necessary that donors and all organs procured – or to be procured – are characterised properly before transplantation. Characterisation is extensively described in this chapter, which focuses on deceased donation after determination of death by neurologic criteria (DBD) and by circulatory criteria (DCD). Specific issues to be considered in DCD (in contrast to DBD), either as uncontrolled DCD (uDCD) or controlled DCD (cDCD), are highlighted in Chapter 15.

Firstly – after all relevant information on the characteristics of the donor and of each organ has been collected from a variety of sources (the 'donor and organ characterisation') – a general assessment of the donor helps in drawing conclusions about the risks of disease transmission to the potential recipient. Secondly, the quality of each potentially donated organ must be considered, based on all data obtained during the organ-specific characterisation process – this second step is covered in Chapter 7. Based on the conclusions extracted from characterisation of the donor in general and of the individual organs, decisions can be made on whether any particular recipient might benefit from the transplantation of each single organ or not, as well as decisions on how the organs will be best procured, preserved and allocated.

The general selection criteria for donors and specific selection criteria for organs intended for transplantation have been changing in recent decades and they will continue changing in future. On the one hand, success in medical science may change the risk of transplantation failure in certain donor populations (e.g. donor age in kidney transplantation). On the other hand, rigid selection criteria may limit the transplantation of organs that might not be beneficial for one particular recipient, but might be life-saving for another after balancing the perceived risk with the benefits for the individual recipient [1-12]. Note that, when assessing the co-morbidity burden of the pool of potential donors, an increased rate of donor referrals may not result in an equivalent increase of actual donors [13], but this finding underpins the need for the donor assessment process to be optimised in its structure to keep workload in an acceptable range.

It is difficult to determine a priori where the absolute limits are regarding any individual donor, and there are relatively few 'absolute contraindications' to donation wherever recipients exist whose survival without an immediate transplant is unlikely. In such cases, in addition to informed consent (Chapter 19) it is best practice to document in the patient's file why such decisions have been taken, within an appropriate study protocol or in exceptional cases in a reproducible intervention protocol that can undergo biovigilance monitoring (Chapter 16). The different stakeholders should consider the principles of communicating risks as outlined in Chapter 19. For com-

munication with people not directly involved in the donation process it is essential to distinguish between the individualised approach – aiming to help one particular recipient with a graft considered otherwise unsuitable for transplantation in many other recipients, which may require specific communication with donor relatives (Chapter 4) – and communication with others inside and outside the hospital to enable them to understand the particular circumstances that warrant use of a seemingly unacceptable organ for transplantation.

Identification of possible organ donors is the starting point for donor evaluation, and should include any patient who meets specific clinical triggers or fulfils certain specific clinical criteria, which have resulted in or may result in death (DBD) as outlined in Chapter 2. All such patients should be referred to the local donor co-ordinator or donor organisation for discussion and evaluation of the possibilities for organ donation (see Chapter 2). Non-referral of any potential donor by the responsible physician in charge should not occur.

The same applies to any patient for whom withdrawal of life-sustaining therapy is planned because therapy is no longer deemed to be in the best interests of the patient. In such cases, cDCD should be considered, when allowed within a given jurisdiction. In cases of termination of unsuccessful CPR (cardio-pulmonary resuscitation), uDCD can be considered when allowed by national law. In both types of DCD, some aspects of donor evaluation may vary from what is described in this chapter and what is outlined in Chapter 12 (§§12.2.6, 12.2.7, 12.3.8, 12.3.9 and Table 12.2, 12.3 and 12.4). For the additionally required details relevant to living organ donors, see Chapter 17. The characterisation of tissue and cell donation is described in the *Guide to the quality and safety of tissues and cells for human application*. In order to avoid repeating information, details about donor transmission risks are covered in chapters 8–10 of this Guide.

Tissue donation should be considered in every person dying in hospital. It is beyond the scope of chapters 6-10 of this guide to discuss all specific issues of tissue donation. Please refer to the *Guide to the quality and safety of tissues and cells for human application* of the Council of Europe in its most recent edition [14]. Notice that tissue donor selection criteria are more restrictive than organ donor selection criteria due to the fact that specific organs can be assigned to a particular recipient in a one-to-one fashion based on an individual risk–benefit assessment, whereas in tissues no prospective assignment is possible and after processing the tissue may be assigned to multiple unknown recipients. Therefore, as with blood transfusion, risk–benefit assessment for tissues is different from that for organ donors.

There are four major categories of risk factor limiting the outcome of transplantation:

a. Not receiving an organ in time is the greatest risk in transplantation from the point of view of a recipient (see §6.1.1).

b. The general risk of transmission of donor disease to the recipient, e.g. infections or malignancies (§6.1.2 and chapters 8 to 10).

c. Donor or organ characteristics that increase the likelihood of graft failure after transplantation in the short and long term (§6.1.3 and Chapter 7).

d. Risks related to recipient characteristics, the transplantation process, immunology etc. (§6.1.4).

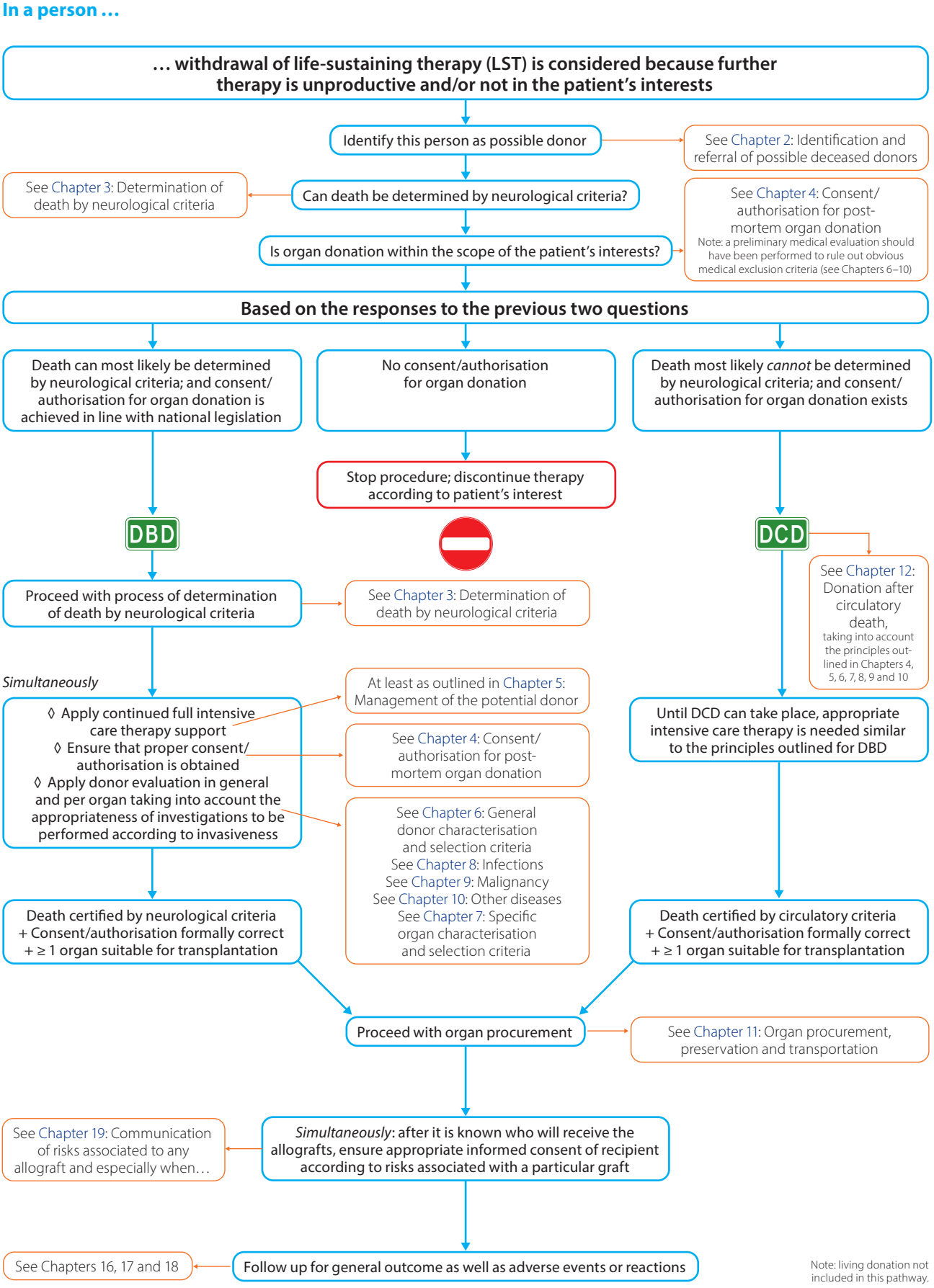
One challenge in donor characterisation, assessment and selection is that the investigating physicians may focus pre-emptively on risk factors that limit the outcome of transplantation of single organs – e.g. lung or kidney – instead of first reviewing all details to get an overview of the donor and all organs. Sections 6.1.1 to 6.1.3 summarise the impact of donor and organ characterisation and selection on the outcome of transplantation, while sections 6.2 to 6.8 and Chapter 11 review the principles of donor and organ characterisation, assessment and selection. Figure 6.1 highlights the donation–transplantation process where donor and organ characterisation takes place.

6.1.1. Risk assessment of general donor – not receiving an organ in time

The greatest risk for a patient awaiting transplantation is not receiving an organ in time before their health status deteriorates to a condition where transplantation may not be helpful any more. The inclusion criteria for organ donors have been widening continuously because growing experience has shown that the individualised risk–benefit assessment for each donor–recipient combination gives the best chance of achieving a successful outcome for a recipient. Therefore deselecting possible donors early upon identification without appropriate evaluation increases the risk of missing out on a potential transplant [15].

Figure 6.1. **Donation and transplantation process in relation to the contents of this guide**

Note: donor and organ characterisation accompany the process at multiple stages.



6.1.2. Risk assessment of general donor – disease-transmission risks

According to the EU-funded Alliance-O project, 'non-standard-risk donors' are defined as those in whom the risk of disease transmission to the recipient is estimated as: unacceptable; increased but acceptable; calculated; or not assessable [1]. Based on data collected in 11 European countries within the EU-funded Dopki project, it can be concluded that non-standard-risk donors have not been uniformly considered throughout the EU [2]. Some member states have prevented the transplantation of organs from such donors by means of legal or technical provisions, whereas others have followed specific protocols for using organs from these donors. Based on the knowledge gathered in countries where such donors are used, it can be concluded that more organs from non-standard-risk donors could be used than have actually been used [1-2].

The majority of deceased donors nowadays suffer from severe cerebral damage due to different kinds of cerebro-vascular incidents. In many countries, more than 50 % of deceased organ donors are above the age of 60 years [16]. There is an increased risk of transmission of undetected and untreated malignancy in this older donor group, based on growing knowledge that selected donors with confirmed malignant disease can be accepted (see Chapter 10). In the case of a malignancy known or detected in a donor, it may be graded as minimal risk, low to intermediate risk, high risk or unacceptable risk according to the estimated probability of transmission (see Table 9.4).

The risk of transmission of infections depends on the modified prevalence of pathogens due to climate change or higher global mobility of people or presence of animals etc. as well as the availability of new drugs to treat or prevent infections (see Chapter 18). Regarding the risk of infectious disease transmission in non-standard-risk donors, physicians have to carefully balance whether pre-emptive and/or post-exposure treatment of the pathogen is possible in the recipient without harm, especially taking into account whether an appropriate therapy for such infection is available or not. Where new treatments are developed, acceptance criteria for donors or particular donor–recipient combinations may change rapidly, as has been seen with the advent of curative treatment for hepatitis C.

Other rare disease-transmission risks that may also exist are outlined in Chapter 19.

Based on careful assessment of donors, transplant physicians have to weigh the risk of disease transmission against the risks of remaining on the waiting list. By refusing an allocated organ, the patient might die or their clinical condition might deteriorate to the extent that transplantation is no longer feasible.

In non-standard-risk donors the Alliance-O classification of risk levels will not be used any more in this guide for grading disease-transmission risk [2-3]. Experience from the previous editions of this Guide [15] has shown that this static classification does not help to describe the most appropriate consideration of all individual donor and recipient factors for final risk assessment. After proper risk–benefit analysis based on the needs of an individual recipient, a generalised statement about assumed absolute contraindication to organ donation or classification as unacceptable risk [1] becomes very difficult. Taking into account the limited number of organs available, compared to the number of patients requiring a life-saving transplantation, accepting a life-saving organ in the absence of other therapeutic options should be justified on a case-by-case basis if this is the only reasonable option for possible survival of the recipient. Therefore two groups of donors may be defined:

a. Standard risk donor: after donor characterisation, no clinical evidence exists for increased disease-transmission risks beyond the population-adjusted average risks for undetected diseases.

b. Non-standard-risk donor or increased-risk donor: after donor characterisation, clinical evidence exists for an increased transmission risk of a particular disease beyond the population-adjusted average risks for other undetected diseases. In this case a targeted risk–benefit assessment of each matched donor–recipient combination is required in order to identify whether transplantation of this graft into this particular recipient will be without harm, or with acceptable harm, to the recipient when compared with the risk associated with not transplanting to the recipient. In this context, the risks of receiving a graft with increased probability of disease transmission should be communicated properly as outlined in Chapter 19. Informed consent in such cases demands appropriate communication of the risk and its documentation in a case-specific manner. In this context the phrase 'unacceptable risk' may apply to conditions where the average recipient without dire medical condition should not receive a graft from such a donor outside a controlled study protocol or appropriate description of what has been done to communicate and accept the risks assumed

unacceptable. The phrase 'accepted risk' (named in some publications 'calculated risk') may apply to conditions where the average recipient without dire medical condition may receive a graft from such a donor within a controlled study or established treatment protocol under continuous evaluation about safety and with informed consent.

6.1.3. Risk assessment of the likelihood of failure associated with a specific graft

The assessment of the risk of failure of a particular graft is discussed in more detail in Chapter 7 and is beyond the scope of this chapter. However, general donor assessment and selection is biased by the focus put on the limited function or quality of one or more single organ(s). The best practice is

a. firstly to assess the general and formal issues discussed in sections 6.2 to 6.8, and then
b. secondly to proceed to the assessment of each individual organ as outlined in Chapter 7.

Whenever there is a chance that at least one organ may be finally transplanted, assessment of the donor should proceed. The issue of assumed reduced graft quality is summarised by the phrase 'expanded-criteria donor' (ECD). Unfortunately, donors with otherwise optimal organ quality, but with the above-mentioned disease-transmission risks (§6.1.1), are labelled in some studies as non-standard risk donors whereas other studies merge them in this ECD category. Therefore, this inconsistent inclusion of cases into the ECD concept may result in an unacceptably high discard rate of organ donors due to imprecise wording.

The concept of ECD was initially developed in the US by the United Network for Organ Sharing (UNOS) to account for the fact that not all deceased donor kidneys provided similar transplant outcomes, but their use increased the donor pool providing grafts for transplantation [17]. Still there is no clear, unambiguous and widely accepted definition of ECD. Difficulties arise on how to define ECD, reflecting different thresholds for different organ types and the increased use of less than ideal organs such that what was considered an ECD yesterday is now more typical of a 'standard' donor today. [6, 10, 15-22]. Currently the Eurotransplant region uses a set of parameters to define ECD criteria for liver donors [23], but over 50 % of the donor livers are classified as marginal when following these criteria [24]. A similar phenomenon has been noted in the UK [25].

The use of a dichotomous term such as ECD does not reflect the fact that the quality of a graft may depend on many donor factors (see Chapter 4). In addition, graft outcomes are affected further by transplant and recipient factors, making graft quality *per se* difficult to measure. The broad spectrum of graft quality runs from optimal quality to not transplantable, with much variation in between. Therefore, graft quality would be best described by a continuous score. Such continuous scoring tools have been developed, using data derived from national transplantation registries (UNOS/SRTR; NHSBT), such as the liver donor risk index (LDRI) for livers, the kidney donor risk index (KDRI) for kidneys and the pancreas donor risk index (PDRI) for pancreas [4-5, 11], and these donor risk scores may then be used in organ allocation. However, calculated overall donor quality in Europe seems to be less optimal than in the US [6, 15, 24, 26], probably in part because donor age is different and this is one of the most influential factors determining risk of graft failure. Therefore, data retrieved from registry studies in the US may not be transferable to the European context [26]. While some studies were able to confirm the usability of such donor risk indices [27], others could not find a clear correlation between outcome and donor risk index [6, 24, 28-34]. Also, recent studies have failed to show an increased utilisation of kidneys from ECDs after the introduction of the KDRI in kidney allocation [35], although from a pragmatic viewpoint such grafts could be used in appropriately selected recipients.

As an example of taking into account some of the above-mentioned issues, the Eurotransplant Senior Program matches kidneys from donors above the age of 65 to recipients above the age of 65 years: because kidneys procured from advanced aged donors are at increased risk of long-term failure, these are preferentially used for elderly recipients. In such a way the assumed limited duration of graft function can be matched to the assumed limited life expectancy of elderly recipients [7-8]. This concept takes also into account the fact that kidneys procured from elderly donors will be compromised by further exposure to long ischaemia times by the use of specific allocation rules.

6.1.4. Risks not associated with the donor or the graft donated

Further risks for transplant recipients are those associated with the transplantation procedure (including the issues of extraction from the donor, organ preservation and ischaemia times), their condition before the procedure, the operation itself and the subsequent care period. Acute and/or chronic re-

jection of organs can occur and add to the risks of early graft loss. Presentation of complications due to immunosuppressive therapy can increase, particularly if extended and more potent immunosuppressive protocols (using mono- or polyclonal antibodies as induction therapy) are used, such as re-activation of *Cytomegalovirus*, complications associated to other viral infections asymptomatic in the donor (e.g. latent Epstein–Barr Virus infection and its associated risk to post-transplant lymphoproliferative diseases) as well as complications from pre-existing (and presumably cured) malignancies.

Precise data about previous immunisation against human leukocyte antigen (HLA) and the risks of developing donor-specific antibodies that may prejudice the current (and any future) transplant are important issues to consider before and after transplantation (see §6.6).

Little is known about the frequency of, or the reasons for, recurrence of primary diseases leading to organ failure. There are very well-known diseases, such as primary focal and segmental glomerulosclerosis, with a high risk of disease recurrence in the kidney graft. However, there are almost no data available on what kind of donor- or recipient-related factors influence the rate and risk of recurrence of primary diseases.

6.2. General evaluation of deceased organ donors

Once a potential donor has been identified, and after all relevant formalities and documentation have been properly managed, the priority is to establish their suitability by appropriate donor evaluation. To do that, the following sources of information should be used, with the aim of reconstructing the donor's current and past medical and social history as accurately as possible.

a. Interviews with the family, relatives and/or friends and all other relevant sources (see appendices 10 and 11 for examples of standardised forms),
b. Interview with the attending physician and nurse, as well as other healthcare providers and the responsible general practitioner/family doctor according to the formal and informal rules in the particular national healthcare systems,
c. Detailed review of current and past medical notes/electronic files,
d. Assessment of the donor's medical and behavioural history by review of all written reports about previous diseases (e.g. including histological tumour diagnosis, stage, treatment, follow up) etc.,
e. Full physical examination, including exact measurement of height and weight if possible,
f. Laboratory tests, including all relevant microbiological testing (specific note should be made of assays with pending results to be followed up post-procurement),
g. Complementary investigations (e.g. ultrasound, echocardiography, ECG, CT scan, histopathology etc.) as indicated,
h. Autopsy if to be performed: not possible before procurement, but results must be supervised and communicated to the organ procurement organisation (OPO) immediately.

6.2.1. Donor history

The term 'donor history' covers the fact that all medical, social and behavioural data are collected properly and provided for further assessment (see §6.3 and Table 6.4).

6.2.1.1. *Donor evaluation*

The history of an organ donor must be obtained with respect to all kinds of transmissible diseases and any disease that may affect organ quality. An interview with relatives of deceased organ donors should be undertaken (see appendices 10 and 11), bearing in mind that, under emotional stress, they might omit, forget or mix up details. However, adding any stress to grieving relatives should be avoided. Contact with the general practitioner of the donor has been proved helpful, alongside a review of hospital archives for historic data or other sources of information (e.g. Cancer Registry). Finally, written reports clearly describing details of previous diseases should be obtained to perform an objective risk assessment.

In order to minimise the risk of unexpected disease transmission, it is important to obtain data on history of travel or residence, including information about living conditions, migration background, refugee status (e.g. stay in camps or elsewhere, or refugee route) and work places (environment: e.g. sewage plant, woodlands, farm, mines, airport, hospital, foreign countries). Also, check history of contact with SARS-CoV-2 infected people or associated risks (see Chapter 8). This may help to identify risks related to places/countries with inferior hygiene standards or with a high prevalence of certain infections, or where the environment poses other risks to health or organ function. With the same aim, information should be obtained about hobbies (e.g. home, garden, animals, woodlands), drug abuse (e.g. intravenous drugs,

needle sharing, intranasal cocaine sniffing, oral or recreational drug consumption, alcohol, smoking) and lifestyle (e.g. multiple sexual partners, commercial sex worker, sexual contacts or imprisonment). This information may require further investigation.

The donor profile evaluation should document the donor's medical and behavioural history, including general data such as age, gender, body weight, height, cause of death, ICU care and results of physical examinations and laboratory tests (see §6.2.2, §6.2.3, Table 6.1 and Table 6.4).

6.2.1.2. *Clinical evaluation*

In addition to the information in the donor profile, the clinical evaluation should also include information on the haemodynamic status of the donor, in particular asystolic, hypotensive or hypoxic episodes, need for cardiac resuscitation, use of inotropic or vasoactive drugs and duration of mechanical ventilation, as well as results of clinical examinations and laboratory tests (see §6.2.3 to §6.2.5, Table 6.1, Table 6.2 and Table 6.4).

These parameters are all needed to assess, firstly, the suitability of the deceased person as an organ donor and, secondly, the suitability of a specific organ (see Chapter 7). This evaluation includes all diagnostic investigations performed, such as X-rays (especially thorax), CT scans (especially head, thorax and abdomen), ultrasounds (especially abdomen), histopathological examinations, echocardiography, coronary angiography and bronchoscopy (see §6.2.3 to §6.2.5, Table 6.2). In this context it is helpful to document the results of any investigations performed previously, beyond the scope of donor evaluation, in order to clarify current findings (see Appendix 15).

Standardised questionnaires should be used to obtain the information outlined in Table 6.3, and as shown in the examples of appendices 10, 11 and 13. The information obtained must be merged into the clinical data outlined in section 6.2.6 (see chapters 8, 9 and 10 for further details about which information must be considered from the viewpoint of risks related to transmissible diseases). If any information is not available or cannot be obtained properly, then the transplant teams must be informed in order to assess the risks associated to this information gap.

It is the responsibility of the person or team performing the procurement surgery to document and forward information on any abnormal findings observed during the procurement procedure (see §6.3 and Chapter 11).

Proper donor maintenance should start as soon as possible, ideally while appropriate formal consent is being obtained where national legislation permits, and definitely once death has been certified and consent gained, in order to maximise the chances of successful organ procurement and post-transplantation function (see Chapter 5). Note that donor management should follow accepted recommendations and guidelines, although appropriate critical care therapy in any patient with cerebral lesions already covers all key aspects of proper donor maintenance. As donor maintenance is strongly associated with organ quality and function, data on donor care should be recorded and documented continuously (see §6.2.3 and Table 6.4).

A comprehensive summary should be prepared of all clinical data and information obtained, to be easily understood by a third party (e.g. transplant centre performing risk–benefit assessment for an organ offered); for an example of an information form for this purpose, see Appendix 12. In cases of abnormal findings, with further investigations having been undertaken, results must be included in the donor documentation as described in sections 6.2.2 to 6.2.6. Where no abnormal results exist, a note to document what investigations have been undertaken should be made.

Notice that the following points may turn out to be critical in donor evaluation:

a. Encephalitis or neurologic/mental/psychiatric disorder of unknown aetiology, as well as any fever, rash or discomfort, unexplained weight loss etc. should be a signal to check for transmissible disease (see chapters 8 and 9). This should not be restricted to donors with a history of travel abroad.

b. Intracranial metastases should always be taken into account in donors diagnosed with intracranial haemorrhage, especially if no evidence of hypertension or arterio-venous malformation exists. Primary intracranial cancers have a biologic behaviour different to that of solid organ cancers or haematological malignancies (see Chapter 9).

c. After all data have been collected and cross-checked against the donor and the organ-specific selection criteria, as outlined in chapters 7-11, a plan must be set up to organise the procurement and to decide which complementary tests must be performed before, during or after procurement.

6.2.2. Physical examination

Physical examination should consist of a recent *ante mortem* external examination of the donor, including a limited internal examination during/after

procurement, to look for evidence of high-risk behaviour, unexplained jaundice, hepatomegaly, hepatitis or other infection, neoplastic disease or trauma (e.g. check for old/new scars, healed/purulent wounds, exanthema, rash, injections, palpable space-occupying lesions) and breast examinations and digital rectal examinations (DRE) for each donor should also be done. Tattoos and piercings are common; the sole issue is whether they were applied under sterile conditions or not recently (see §8.3; check when, where and how the tattoo was performed). The information obtained through physical examination is complementary to the comprehensive summary of clinical data as outlined in section 6.2.6.

There are three important points to notice:

a. Surgical scars are very important to note, e.g. they can hint at previous operations of which neither the relatives nor the general practitioner were aware, and which may have been previous oncologic operations.

b. Exact measurements of body height (always possible) and body weight (often possible) help to avoid size mismatch during allocation for recipients [36].

c. Note that physical examination should be complemented by thorough examination of all organs in the thoracic and abdominal cavities during the organ procurement (e.g. oesophagus, stomach, intestine, lungs, prostate, uterus, adnexa; see §6.4) as well as autopsy if possible.

An international protocol of physical examination in tissue donation is shown in Appendix 12 of this Guide (equivalent to Appendix 14 in the 4th edition of the *Guide to the quality and safety of tissues and cells for human application*). This protocol may also be applied to organ donors. In the case of abnormal findings, escalation with further investigations should be carried out [37]. The limited sensitivity and specificity of physical examination for discovering pathologies must be taken into account. Therefore additional investigations before and/or during procurement are mandatory (see §6.2.2 to §6.2.5).

6.2.3. Laboratory tests

All laboratory (lab) tests should be carried out before cessation of circulation. It is advisable to report the time when samples were taken, as well as medical interventions and clinical data. For appropriate interpretation of changing lab parameters in summary during the actual course of disease, see section 6.2.6.

All data collected since admission to ICU should be reported continuously. For the assessment of organ function, a representative set of data at different time points is sufficient so that any changes during the donation process can be observed (e.g. admission, every second day, most recent values, most extreme values). It is also helpful to know any lab data obtained before hospital admission which may allow better interpretation of an abnormal test during the development of brain death (e.g. a recent record of normal kidney function and no albuminuria in an elderly donor with diabetes now exposed to acute kidney injury after prolonged cardio-pulmonary resuscitation).

In the case of lab parameters, the units of measurement should be clearly communicated. Although many parameters are standardised in their measurement, deviations from assumed reference ranges and units of measurement exist even between hospitals within one region, as well as between countries. Furthermore, the range of values typical for organ donors with all their organs used for transplantation varies dramatically from the reference range assumed for healthy individuals not hospitalised in an ICU.

6.2.3.1. *Screening and available data*

The informative value and clinical relevance of important lab parameters are summarised in Table 6.1. Some remarks about screening for infectious diseases and other lab data are necessary:

a. If a deceased donor received *ante mortem* transfusions (whole blood or blood components), colloids or crystalloids during the 48 h preceding death, a specimen without dilution should be used for testing for infectious diseases. For further details about handling this issue, refer to Chapter 8. It is important to remember that some trauma victims arrive at hospital in an already haemodiluted state. In the course of subsequent intensive care therapy, a significant degree of haemodilution by crystalloids is standard. Replacement of a relevant acute blood loss should be considered in this context. Nevertheless, haemodilution should never be used as an excuse to discard a donor unless there are other risk factors, as outlined in Chapter 8. Note that a donor may acquire antibody reactivity passively by blood products transfused.

b. Specimens drawn from various sites (including blood) for microbiological investigation may help to explain or exclude bacterial or fungal infections. The culture technique used to investigate specimens drawn for microbiological investigations should allow for the growth of aerobic and anaerobic bacteria and fungi. The results should be documented in the donor

record and must be communicated to the donor co-ordinator, OPO and recipient centres immediately upon arrival.

c. Every donor must be screened for HIV, HBV and HCV. Testing for other pathogens should be considered, based on the current epidemiological situation. The results must be available before procurement and before any organ of the donor is used for transplantation as outlined in Chapter 8 (see also Table 6.4). Nucleic Acid Testing (NAT) is preferred where indicated. Importantly, even when using the best screening method available, the incubation period and the diagnostic window period for any infection must be taken into account. Other tests are required in specific situations, in the case of an immunosuppressed recipient or according to national provisions (see Chapter 8).

d. There is a long list of infectious diseases that have been transmitted with organs, as outlined in Chapter 8. The presence of a transmissible disease should not be an automatic reason for excluding a potential donor: once known, it is an element in the allocation process, an element in the correct decision by transplant teams to proceed (or not) with transplantation and an element to be carefully monitored in the different patients transplanted with organs from such a donor. For further details about best practice in donor screening, see Chapter 8.

e. ABO blood group, Rhesus Rh(D) group and HLA-typing: in cases of HLA-typing, molecular-biologic techniques should be used that provide appropriate information for a virtual cross-match (see §6.6).

f. The routine screening of tumour markers is not recommended. In the case of a previously treated malignancy in the donor history where tumour markers were previously used to monitor disease remission, values available from previous examinations and a current update may help to assess the state of disease (see Chapter 9).

g. The other laboratory parameters outlined in Table 6.1 contribute further to donor characterisation. This Table 6.1 contains all lab data that are informative for general donor characterisation and organ-specific issues. Many hospitals use point-of-care systems as well as specific profiles covering a set of specific investigations (e.g. admission status, liver profile, kidney profile, heart profile). Such profiles are in line with the parameters needed to characterise an organ in detail. Depending on the infrastructure of the hospital, not all investigations will be available on a 24/7 basis. This should not be used as an argument to delay a donation procedure.

Table 6.1. **Informative value and clinical relevance of laboratory parameters in donor and organ characterisation**

Notice that hospitals apply individual lab reference ranges adjusted to their local environment. Age and gender adjustment must be considered. Acceptable reference ranges for DBD and DCD have not yet been defined. Lab values are informative only after serial measurement in context of all other clinical data for assessment of organ function.

In the Organs column, Basic refers to basic assessment of any donor whereas organ-specific information is indicated by KI for Kidney, LI for liver, PA for Pancreas, IN for intestine, HE for heart and LU for Lung; if an organ or Basic is in **bold** type, it means the parameter is important for that organ or for basic assessment; for anything else named in that column, the parameter is relevant. Whenever basic and organ-specific assessment is indicated, then beyond the scope of basic assessment this value will be also of organ-specific interest. If not otherwise stated, all measurements refer to the blood compartment.

Parameter	Organs	Comment on informative value and pitfalls associated with measurement
Hb	**Basic**	In intensive care medicine, transfusion threshold is lowered to 7-9 g/dL (4.4-8.6 mmol/L, 70-90 g/L) according to age and cardiac status; down to this range, haemodilution is acceptable
Hct	**Basic**	In intensive care medicine, transfusion threshold is lowered to 20-30 % (0.2-0.3) according to age and cardiac status; down to this range, haemodilution is acceptable
Leukocytes	**Basic**	Acute elevation due to brain-stem coning (therefore, not directly representative for monitoring of infection); elevation if inflammation occurred for multiple causes (e.g. SIRS in brain death)
Platelets	**Basic**	Elevated after brain damage, decreased due to bleeding or coagulation disorders or sepsis; substitution indication exists only in cases of bleeding due to thrombocytopaenia
Erythrocytes		Not important for organ characterisation
Na^+	**Basic**	Hypernatraemia is a complication caused most likely by diabetes insipidus. This should not occur during proper intensive care therapy
K^+	**Basic**	Consider kidney function
Ca^{2+}		Not important for organ characterisation

Parameter	Organs	Comment on informative value and pitfalls associated with measurement
Cl^-		Not important for organ characterisation
Glucose	**Basic**, PA	Acute decompensation during intensive care therapy possible, not representative for time before hospital admission. For PA to be considered properly in relation to ongoing glucose infusions and the general ICU situation.
Creatinine	**Basic**, **KI**, LI	Dependent on fluid load; elevated in kidney failure or due to muscle damage or cardiac failure (chronic)
Urea	Basic, KI	see Creatinine (usually not considered important)
LDH (IFCC 37 °C)	Basic, KI, LI, PA, IN, HE	Tissue damage (necrosis, unspecific), e.g. helpful in donors with suspicion of tissue necrosis (as after asystole, CPR etc.)
CPK (IFCC 37 °C)	**Basic, KI**	CPK is released by muscle damage, which may secondarily harm the kidney after tissue necrosis (like LDH)
CKMB	Basic, HE	Troponin more sensitive/specific for myocardial damage; CKMB also elevated by brain damage (like LDH)
Troponin	**HE**	Increased in myocardial muscle damage
AST/SGOT (IFCC 37 °C)	**Basic**, KI, **LI**, **PA**, **IN**, **HE**	Myocardial damage or liver damage; see ALT
ALT/SGPT (IFCC 37 °C)	**Basic**, KI, **LI**, **PA**, **IN**	Liver cell damage
γGT (IFCC 37 °C)	**KI**, **PA**, **IN**	Liver: indicator of biliary tract damage e.g. acute hypoxaemia, chronic alcoholic/non-alcoholic steatohepatitis (cholestasis)
Bilirubin tot.	Basic, KI, **LI**, PA	Consider if increased in cases of trauma and poly-transfusion due to bleeding or liver damage (cholestasis)
Bilirubin dir.	Basic, KI, LI, PA	
Alk. Phos. (IFCC 37 °C)	Basic, LI	Liver or bone damage or: physiologically elevated in growing children and pregnancy (and in liver transplantation)
Amylase (only pancreas-specific)	Basic, KI, LI, **PA**	Nonspecific (infusion, head trauma, hanging) if not measured as pancreas-specific amylase or lipase; reference range varies between hospitals as measurement is not standardised; only pancreatic-amylase is important
Lipase	**PA**, **IN**	Reference range varies between hospitals as measurement is not standardised, but more specific for pancreas than amylase
HbA1c	**PA**	Informative in PA, not directly affected by ICU care or brain death; limited 24 h/365 days availability in many hospitals; is affected by transfusion.
Tot. Protein	Basic	Consider haemodilution
Albumin	Basic	Consider haemodilution; must be viewed in the context of donor management as well as liver function
Fibrinogen	Basic	Increased due to brain damage or inflammation
Quick PT	**Basic**	Distorted by bleeding and coagulation disorders due to brain damage or therapeutic anti-coagulation after correction by FFP infusion
INR (international normalised ratio)	Basic, LI	Measurement not adjusted to liver function; used in anti-coagulation therapy in people with normal liver function
APTT	**Basic**	Distorted by bleeding and coagulation disorders due to brain damage or therapeutic anti-coagulation after correction by FFP infusion
AT III (antithrombin III)	Basic, LI	Must be viewed in the context of bleeding disorders as well as liver function
CRP (C-reactive protein)	**Basic**, HE, LU	Acute elevation due to SIRS after brainstem herniation possible; not directly representative for monitoring of infection
FiO_2	**Basic**, LU	Must be viewed in the context of respiration therapy as well as other acute events
PEEP	**Basic**, HE, **LU**	
pH (Blood acidity)	**Basic**	
$PaCO_2$	**Basic**, LU	
PaO_2	**Basic**, KI, LI, PA IN, HE, LU	
PaO_2/FiO_2	**LU**	Oxygenation index representative for quality of lung

Parameter	Organs	Comment on informative value and pitfalls associated with measurement
HCO_3	**Basic**	Must be viewed in the context of respiration therapy as well as other acute events
BE (Base Excess)	**Basic**	
O_2 saturation	**Basic**	
Lactate	**Basic**, LI, PA, IN, HE	Indicates tissue damage due to anaerobic metabolism, sepsis, metformin-medication, shock, acute liver or kidney failure; usually raised due to hypovolaemia
Cholinesterase	**LI**	Liver synthesis (exceptionally documented in some countries)
Procalcitonin	Basic	Acute elevation due to brain-stem coning, so not representative for monitoring of infection
Pro-BNP	Basic	Not evaluated in DBD populations; can be indicative of right heart failure, but distorted by fluid overload or acute kidney injury
Blood culture	**Basic**, KI, LI, PA, IN, HE, LU	Bacteria and fungi; anti-microbiological resistance pattern
Urine culture	**Basic**, KI	Bacteria and fungi; anti-microbiological resistance pattern
BAL culture	Basic, **LU**	Bacteria and fungi; anti-microbiological resistance pattern
Other cultures	Basic	Bacteria and fungi; anti-microbiological resistance pattern
Multidrug-resistant bacteria	**Basic**, KI, LI, PA, IN, HE, LU	Screening useful, in many places obligatory as best practice
Urine glucose	PA	Depends on blood glucose; kidney damage (for PA test serum glucose)
Urine protein	KI	Slight proteinuria possible due to urethral-catheter; kidney damage; only data of pre-hospital time during steady-state care can be informative; according to KDIGO Guidelines, albuminuria should be investigated instead of total proteinuria [38]; also the ratio urine protein/urine creatinine is a simple parameter resistant against sampling errors compared to collecting urine for 12 h or 24 h
Ratio urine-protein/ urine-creatinine	KI	< 500 mg Protein/g Creatinine in urine normal, > 1000 mg Protein/g Creatinine indicative of kidney damage if measured in a steady state outside ICU [37]
Urine albumin	**KI**	For assessment of glomerular function more indicative than protein (KDIGO Guidelines) [38]
Ratio urine-albumin/urine-creatinine	**KI**	< 30 mg albumin/g Creatinine normal; > 300 mg albumin/g Creatinine indicative of kidney damage if measured in a steady state outside ICU [38]
Urine Hb	KI	Haematuria possible due to urethral-catheter, but may represent renal tract malignancy
Urine sediment	KI	Exclusion of relevant haematuria, bacteriuria or glomerular or tubular damage
Urine nitrite	KI	Bacterial infection of urinary tract possible
Estimated creatinine clearance or eGFR		Estimates of creatinine clearance or glomerular filtration rate (eGFR) have been developed for screening outpatients in a stable state without haemodynamic changes; therefore, estimates may be inappropriate for use in organ donors; according to KDIGO Guidelines, only measurements in a steady state (probably not during donor care) are reliable [38]
Measured creatinine clearance or eGFR		After haemodynamic stabilisation of a donor, recovery of kidney function can be assessed by this measurement (after one hour); further estimates may be inappropriate for use in organ donors; according to KDIGO Guidelines, only measurements in a steady state (probably not during donor care) are reliable [38]
Screening for emerging regional or pandemic diseases	**Basic**	See Chapter 8: the actual requirements for targeted screening depend on the pathogen; in new emerging pathogens, *ad hoc* recommendations are released based on the local epidemiology (e.g. WNV, SARS-CoV-2), so no general recommendation can be provided and it must be checked locally day by day
Anti-HIV-1/2	**Basic**	See Chapter 8
HIV-NAT		
Anti-HCV	**Basic**	
HCV-NAT	Basic	
HBsAg	**Basic**	
Anti-HBc	**Basic**	
HEV-NAT	Basic	
Anti-CMV; Anti-EBV; Anti-Toxoplasma	**Basic**	

Parameter	Organs	Comment on informative value and pitfalls associated with measurement
Syphilis test	**Basic**	See Chapter 8
Further tests for infections	Basic	
Microbiological cultures	Basic	

Abbreviations

ALT: alanine amino transferase. APTT: activated partial thromboplastin test. AST: aspartate amino transferase. BAL: broncho-alveolar lavage. BNP: B-type natriuretic peptide. CKMB: creatine kinase MB isoenzyme. CMV: *Cytomegalovirus.* CPK: creatinine phosphokinase. EBV: Epstein–Barr virus. γGT: gamma glutamyl transferase. HbA1c: haemoglobin A1c. HBsAg: surface antigen of hepatitis B virus. HE: heart. IFCC 37 °C: measurement according to methods of the International Federation of Clinical Chemistry and Laboratory Medicine at 37 °C. IN: intestine. KDIGO: Kidney Disease Improving Global Outcomes. KI: kidney. LDH: lactate dehydrogenase. LI: liver. LU: lung. PA: pancreas. SIRS: systemic inflammatory response syndrome.

6.2.4. Other complementary tests

Complementary tests can contribute further to characterising the donor when an indication for the particular investigation exists and if the results are communicated within standardised questionnaires as outlined in Chapter 7. One common language should be used by the investigator performing the test and the recipient centres interpreting the results.

For any organ procurement, as a minimum imaging is suggested as outlined in Table 6.2, which may differ in clinical practice from country to country. For abdominal organs the investigations concerning thoracic organs are not of primary interest, but they are helpful for exclusion of other diseases (e.g. malignancy) or co-morbidities (e.g. arterial hypertension and its relation to left ventricular hypertrophy as an indicator for proper treatment). For thoracic organs a specific indication should exist for performing invasive investigation, e.g. coronary angiography in a donor with relevant risk for coronary artery disease (see Chapter 7). When signs of unexpected atypical findings, space-occupying lesions (SOL), changes suspicious for infection etc. are detected in imaging studies, then special consideration must be given to further exclusion of malignancies (see Chapter 9, e.g. whole-body CT scan), infections (see Chapter 8) or other transmissible diseases.

In whole-body CT scan including head, contrast opacification of cerebral arteries or veins should not be interpreted for the diagnosis of cerebral circulatory arrest because of fundamental technical differences between whole-body CT scan and CT angiography dedicated for the diagnosis of cerebral circulatory arrest. Otherwise, discrepant results may occur, providing false positive or false negative diagnoses of cerebral circulatory arrest on the basis of whole-body examination. Depending on the organs considered for transplantation and on indications for general donor assessment, imaging is done in many centres according to the principles shown in Table 6.2.

Two recent studies highlight the two-sided viewpoints of extended imaging: Firstly Mensink *et al.* [39] showed that whole-body CT imaging contributed to detection of SOL as well as additional information helpful during procurement (e.g. anatomy) at a higher rate and efficiency than abdominal ultrasound only or no imaging. Secondly, Ghorbani *et al.* [40] demonstrated in a randomised trial that, after donor transfer from one place to another, lung recruitment becomes necessary in order to re-compensate the harms caused to pulmonary function due to the transfer process. Taking these two observations together, targeted imaging (e.g. by CT-scan) should be planned well in advance, taking into account the side-effects of transport of the donor from one place to another; for example, when CT-angiography is used within the process of brain death certification, then a complementary whole-body CT scan to obtain raw data for later evaluation may be helpful.

In cases where an examination (e.g. coronary angiography) cannot be performed in a particular hospital, individual decisions become necessary before any organ or donor is lost due to this limitation. It is not usually appropriate to transfer a donor to another hospital just to perform a complementary test. In special cases beyond the standard set of tests, additional investigations may be invaluable (e.g. whole-body CT scan where there is suspicion of malignancy).

In cases of cDCD as well as DBD, these tests can be performed early in the work-up as long as they are not invasive, without harm to the patient and as part of the repertoire of high-quality intensive care medicine according to the treatment protocols. Investigations performed early in the work-up should be re-evaluated according to the principles outlined in Chapter 7. In uDCD only a limited set of investigations is possible in the emergency room according to the standards of emergency medicine. In such cases the quality of measurement results represents the needs of investigations required to decide on further therapy and they do not represent a more detailed

and qualified examination as applied in cDCD or DBD.

6.2.5. Histopathological examinations

All suspected malignant tumours should be investigated by histopathology. The mass should be resected *in toto* (not just parts of it) to rule out or investigate malignancy properly, whenever possible without sacrificing or significantly damaging a graft otherwise suitable for transplantation (e.g. Ro resection in space-occupying lesions in a kidney). Resection of a suspicious mass on the back table should be done after packing away the other organs to avoid cross-contamination. The pathologist should be informed about all donor data and the macroscopic appearance surrounding the suspicious mass, preferably with a photograph to illustrate this (see Chapter 9). In consultation with the investigating pathologist, it should be clarified which medium can be used for transport of the sample sent in for histopathologic examination (based on the assumed transport time).

A question frequently asked is whether, in cases of a suspected brain tumour, imaging or biopsy will be sufficient for an appropriate diagnosis, allowing a release of organs for transplantation. Only in urgent or otherwise difficult circumstances may this be done, since the best practice is to have a full/complete brain autopsy performed with a histopathologic examination (e.g. the brain can be procured for autopsy during or after organ procurement). However, there are certain radiological features that may enable confirmation of the nature of some brain tumours without histology.

It is recommended that in every region or country a network of pathologists is created for the purpose of a 24/7 service to assess biopsies of organ donors. Regional solutions with one centre on duty, e.g. a centre associated with a university hospital that has a transplantation facility, might be helpful. Exclusion of malignancy in SOL and assessment of liver or renal quality are especially pivotal in decreasing organ discard rates. Agreement on standardised wording in documentation is suggested (see Appendix 15).

Finally, it is preferred to have an autopsy of any person who has died, with the aim of knowing all the circumstances of death as well as co-morbidities. Unfortunately in clinical practice it is often difficult to obtain authorisation in many cases. Therefore at least any suspicious SOL in a donor should be removed and examined.

6.2.6. Summary of clinical data

For the comprehensive description of the donor and specific characterisation of the organs, the laboratory test results and clinical data shown in tables 6.1, 6.2 and 6.4 should be summarised in an accessible and comprehensive way, including the information obtained already or later on during the donation process. Importantly, any changes during the process of organ donation should be clearly described. Organ exchange and/or allocation can be performed once this information has been provided as completely as possible, enabling proper assessment. Whenever data cannot be provided properly, despite best efforts, this must be indicated clearly; when donor evaluation has found no evidence for a risk factor, this also should be documented. These data should be updated with the most recent information available, even after transplantations have been carried out. Agreement on standardised wording in documentation is suggested (see Appendix 15).

Table 6.2. **Imaging during donor evaluation with consideration of organ-specific morphology and disease-transmission risks**

	Basic consideration	Transfer of donor to other facility	Kidney	Liver, Pancreas, Intestine	Heart	Lung	(Previous) malignancy	(Previous) infection	Other lesions, acute events
Abdominal ultrasound	limited sensitivity and specificity	bedside	size, morphology, other abnormalities*	size, morphology*	add on*	add on*	basic orientation*		basic orientation*

SOL: space-occupying lesions; LVH left ventricular hypertrophy, LVF left ventricular function, RVF right ventricular function; Add on: complementary in best practice.
* Basic imaging in many countries, † nice to have as imaging in some countries; ‡ depends on indication; § important in case of previous malignancy.

	Basic consideration	Transfer of donor to other facility	Kidney	Liver, Pancreas, Intestine	Heart	Lung	(Previous) malignancy	(Previous) infection	Other lesions, acute events
Chest X-ray	limited sensitivity and specificity	bedside	add on*	add on*	severe calcification*	basic orientation*	huge SOL*	basic orientation*	basic orientation*
CT-Scan (whole body)	SOL, morphology, vessel status (e.g. calcification), vascular anatomy; depends on indication	transfer	morphology, SOL, vessels (e.g. calcification)†‡	morphology, SOL, vessels, (e.g. calcification); split anatomy†‡	coronary artery calcification†‡	atelectasis, SOL, trauma†‡	rule out SOL‡§	infection (e.g. Covid-19)‡	atelectasis, pulmonary embolism, trauma, vascular anatomy‡
Echocardiography	snapshot, serial evaluation	bedside	LVH, interaction with acute or chronic heart disease†	LVH, interaction with acute or chronic heart disease†	LVH, LVF, RVF, valves, acute and chronic heart damage*	side effect of heart function†		haemodynamic assessment†	haemodynamic assessment†
Electrocardiogram	limited sensitivity and specificity	bedside	side effect of major cardiac damage	side effect of major cardiac damage	arrhythmia, major cardiac damage*	side effect of major cardiac damage		endocarditis	haemodynamic assessment
Bronchoscopy	invasive	bedside	improve gas exchange, rule out tumour†	improve gas exchange, rule out tumour†	improve gas exchange, rule out tumour†	intrabronchial status*	review status‡	intrabronchial status†	bronchus cleaning†
Blood gas test (FiO_2 1.0, 10 minutes)	serial evaluation	bedside	add on*	add on*	add on*	gas exchange*			ventilation setting*
Coronary angiography	invasive, requires indication	transfer			intravascular status of coronary artery‡				
Others	depends on indication	depends on method	depends on method	depends on method	depends on method	depends on method	depends on method	depends on method	depends on method

SOL: space-occupying lesions; LVH left ventricular hypertrophy, LVF left ventricular function, RVF right ventricular function; Add on: complementary in best practice.
* Basic imaging in many countries, † nice to have as imaging in some countries; ‡ depends on indication; § important in case of previous malignancy.

Table 6.3. **List of pragmatic questions that might help in assessing whether donors and grafts are suitable for transplantation in cases of a rare disease where insufficient data are available**

Question 1	Was a successful transplant previously carried out where the donor was known to have had such a disease? If so, what was the outcome and how were other organs affected in this recipient? (See e.g. www.notifylibrary.org.) Were all additional resources/sources of information checked? (For example, www.orpha.net for rare diseases, literature.)
Question 2	Are components of immune-suppression protocols used to treat this disease effectively? Can harm to recipient and graft due to immune-suppression be excluded as a possibility? Is specific, successful anti-infective treatment possible in the immunosuppressed recipient of the particular graft in the case of an infectious pathogen, or can disease transmission be prevented successfully?
Question 3	Was the organ itself damaged? Are the supplying vessels intact and suitable for anastomosis? Is the probability high that the organ will function properly in the recipient within an acceptable time interval?

Question 4	Are there any other donor-related risk factors that may compromise the outcome? How does the cumulative effect of all risk factors taken together impact the graft quality?

After going through the questions above, an individual risk–benefit assessment for each donor–graft–recipient combination must be discussed before a decision is made. The decision process should be documented for reproducibility and later sharing of the knowledge (e.g. by prospective application of biovigilance tools according to Chapter 16).

6.3. General donor-selection criteria (pre-procurement)

Only a few absolute exclusion criteria exist for organ donation, but there are increasing numbers of donors with co-morbidities that may compromise graft quality or be transmissible to the recipient. With increasing utilisation of co-morbid donors, knowledge of transmission risks is expanding. However, individual cases may need expert local advice to evaluate their suitability as a donor in general, or as a donor of specific organs – for example, donors with specific infections or malignancies (see chapters 8-9).

Careful consideration should be given to the following conditions, which are considered as general exclusion criteria because no life-saving treatment is available if transmission of the disease to the recipient occurs:

a. Active malignancy with metastatic spread (see Chapter 9).

b. Severe infections that are systemic or of unknown origin (especially any case of encephalitis of viral origin or febrile meningoencephalitis of unknown origin), as well as ongoing sepsis or disseminated, uncontrolled infection (bacterial, viral, fungal, parasitic, active [disseminated] tuberculosis, acute Chagas disease) or infections without any available treatment (e.g. rabies). Specific details are outlined in Chapter 8.

It is highly recommended to refer to chapters 8, 9 and 10 in order to perform a proper assessment of the risk for transmission of infections, malignancies and other rare systemic diseases. As mentioned in the introduction it is pivotal to consider that the decision to use or not to use an organ of a donor is based on the individual risk–benefit assessment of each donor–recipient pair (see §6.1).

There is a long list of infectious diseases that have been transmitted with organs, as outlined in Chapter 8. On the other hand, the presence of a transmissible disease should not be the only reason nor an automatic reason for excluding a potential donor: once known, it is an element in the allocation process, an element of the decision by a transplant team to proceed (or not) with transplantation of a particular recipient and an element to be carefully monitored in the different patients transplanted with organs from this same donor, within connected vigilance systems. There is no reason to believe that a disease could not be transmitted with an organ/tissue, independently of how well the graft has been perfused during preservation. For further details about best practice in donor screening, see Chapter 8.

Similar consideration may apply to situations of a donor with a pre-existing malignancy, as described in Chapter 9 in detail.

Donor age and its associated co-morbidities should be evaluated according to the organ-specific selection criteria (see Chapter 7). Age *per se* is not a contraindication for organ donation, but the biological age will impact on the organ quality and function. Adding avoidable risk factors on top of existing ones should be avoided (e.g. prolonged ischaemia times in elderly donors with co-morbidities). Current donor age criteria should be re-evaluated, as a European registry study showed when comparing outcomes in kidney transplantation by donor age for the periods of 1996 to 2006 and 2007 to 2016 [12].

For any other systemic disease, the pragmatic approach shown in Table 6.2 can be used as guidance on how to handle the case when a rare disease is not covered within the scope of chapters 8-10.

Infections, malignancies and other diseases transmitted with a graft expose the recipient to unexpected and/or unwanted complications. Whether or not it is possible to transplant an organ/graft to a suitable recipient with an associated acceptable risk must be considered before excluding an organ/graft for infectious or other risk reasons. For deceased organ donors especially, there is insufficient time to perform extensive investigations and for results to become available in a timely manner, so strategies have to be applied to reduce the risks as much as possible. However, any deviation from 'normal circumstances' should be considered indicative of a possible undetected risk. Further details are outlined in chapters 8-10. Table 6.4 provides a summary of risk factors limiting successful donation. These should be considered when deciding final conclusions about general donor suitability.

Table 6.4. **Data needed for a comprehensive characterisation of the donor and organs**

In the Data column, the minimum dataset defined in Part A of the Annex to Directive 2010/53/EU is marked by an asterisk (*); the complementary dataset in Part B of the Annex is marked by a dagger (†). For further details, see §6.8.

In the Cross-reference column, refer to the chapter or section (§) specified to see all details that need to be considered.

1. General data (important for allocation)		
Data	**Comment, informative value and background**	**Cross-ref.**
Type of donor*	**DBD, cDCD or uDCD donor**	
Establishment where the procurement takes place and other general data* Contact details of this establishment or of the organ procurement organisation in charge†	Necessary for co-ordination, allocation and traceability of the organs from donors to recipients and vice versa as well as for urgent questions by transplant teams during risk–benefit assessment for a particular recipient.	
Age,* sex,* height,* weight,* other demographic and anthropometric data†	Data may determine allocation of organs (e.g. age match). For heart, lung, liver and intestinal transplantation, the size/weight match between donor and recipient is important. Weight and height should be measured [36] whenever possible.	
Blood group,* HLA-typing	Relevant for organ allocation.	§6.6
Virology/microbiology	All details must be known about the risk of transmissible pathogens, which may determine further allocation of organs. Before any graft is transplanted, anti-HIV1/2,* anti-HCV,* anti-HBc* and HBsAg,* as well as SARS-CoV-2 NAT from upper/lower respiratory tract, must have been determined.	Chapter 8 and §8.2 for indication of additional tests
The correctness of data, e.g. blood group, virology, should be ensured when determined or whenever data are transmitted. Ensure that specimens for the above-mentioned investigations are drawn properly and in time.		§6.8

2. Medical history of acute event		
Data	**Comment, informative value and background**	**Cross-ref.**
Cause of death* Date/time of death*	It is imperative to know the exact cause of death in order to identify possible additional risks associated with the underlying cause of the brain injury. Occasionally, a central nervous system infection is obscured by other causes of death or by an overlap in imaging, with the risk of fatal disease transmission [41]. The following conditions should raise concerns: Cerebrovascular accident without risk factors for stroke, etc. Unexplained fever or illness or altered mental status at presentation/admission with or without unexplained cerebrospinal fluid abnormalities (e.g. pleocytosis, low glucose, elevated protein) Immunosuppressed host (e.g. autoimmune disease, cirrhosis) and/or environmental exposure (e.g. animals) The same applies for verification of a space occupying intracranial lesions (e.g. brain tumours *v.* metastasis).	Chapter 8, Chapter 9 For cerebral infections, see §8.9
Timeline: admission to hospital, admission to ICU, start of ventilation, declaration/verification of death	It is helpful to estimate the chances of recovery from primary critical periods at admission and/or the risk of acquiring nosocomial infections.	Chapter 8
Episodes of cardiac arrest/resuscitation and/or prolonged hypoxia for other reasons	For each episode of cardiac arrest, information on its duration, the duration of CPR and the treatment provided should be collected (e.g. defibrillation, medication), as well as about the haemodynamic status afterwards. Hypoxic episodes (e.g. after strangulation, suicide by hanging) should be documented in the same fashion.	Chapter 7
Hypotensive periods/shock	Duration of hypotension or shock should be reported with systolic and mean arterial blood pressure, as well as medication applied.	

Abbreviations

Anti-HBc: hepatitis B core antibody. BAL: broncho-alveolar lavage. CMV: *Cytomegalovirus*. CPR: cardio-pulmonary resuscitation. DCD: donation after circulatory death. D/R: donor/recipient. EBV: Epstein–Barr virus. HbA1c: haemoglobin A1c. HBsAg: hepatitis B surface antigen. HBV: hepatitis B virus. HCV: hepatitis C virus. HIV: human immunodeficiency virus. HLA: human leukocyte antigen. ICU: intensive care unit. NAT: nucleic acid testing. PEEP: positive end-expiratory pressure. SIRS: systemic inflammatory response syndrome. TPHA: *Treponema pallidum* haemagglutination.

General information/ remarks*	Summary of key information about actual donor data and history. This should cover all information outlined below as well as important remarks or facts to be considered for the further planning of the donation procedure.	

3. Medical history before hospital admission

Data	Comment, informative value and background	Cross-ref.
History of arterial hypertension	Duration, kind and quality/success of treatment may indicate or exclude organ damage (kidney, heart, pancreas, risk of arteriosclerosis). Presence of left ventricular hypertrophy in echocardiography is indicative of quality of long-term care.	Chapter 7
History of diabetes	Diabetes type (insulin-dependent/non-insulin-dependent), duration, kind and quality/success of treatment may indicate or exclude organ damage (arteriosclerosis > kidney? heart?; obesity > liver steatosis?). Valuable information may be obtained by contacting the general practitioner, especially for laboratory tests such as HbA1c, glucose tolerance, kidney function (albuminuria or proteinuria) and other medical interventions due to diabetes. Type II diabetes is a frequent diagnosis in elderly people when patients did seek medical advice. Insulin demand of a donor in an ICU is not indicative of pre-existing diabetes.	Chapter 7
History of smoking	Duration and quantity of smoking (pack-years) may be indicative for cardiovascular damage and risk of smoking-related malignancies.	Chapter 7, Chapter 9
History of alcohol abuse	Duration and quantity of alcohol consumption may be indicative for organ damage (liver, kidney, heart, pancreas, intestine, risk of arteriosclerosis). Chronic abuse combined with malnutrition or smoking is a risk factor for other diseases, including oropharyngeal and oesophageal malignancy.	Chapter 7
History of drug abuse*	It should cover past and current history. Extended virology testing is necessary in cases of drug abuse (e.g. intravenous drug abuse, needle sharing, intranasal cocaine sniffing, oral or recreational drugs consumption), with secondary effects on lifestyle (e.g. multiple sexual partners). Organ damage can be caused by substance abuse.	Chapter 8, in detail §8.2 to §8.3
History of transmissible diseases,* HIV,* HCV,* HBV*	For transmissible diseases, current history is particularly relevant. HBV/HCV: pattern of infection, treatment (medication) and virological response to treatment are informative in concert with the medical history. New treatment regimes in HCV, HBV and HIV will change the exclusion and inclusion criteria for donors and organs with such infections.	For basic donor screening §8.2 to §8.3 and in detail §8.6.11, §8.6.12, §8.6.15
Behavioural risk, commercial sex worker, sexual contacts, imprisonment	This may indicate that organ function could be compromised or that an increased risk of infectious diseases exists. It is necessary to ask about sexual behaviour (e.g. prostitution, frequently changing partners regardless of their sex or gender), use of intravenous drugs or cocaine, lifestyle or imprisonment.	§8.2 to §8.3
Blood transfusions or transplant procedures; body piercing or tattoos; non-medical injections	Risk of blood-borne infections is increased if they occurred within the 180 days preceding death. Body piercing or tattoos are very common nowadays. If they have not been applied professionally under sterile conditions, then they carry the same risk as non-medical injections.	§8.3
History of malignancy*	It should cover the detailed past and current history of all malignancies. Records should be checked for any previously diagnosed neoplasms or tumours removed.	§9.2 to §9.3
History of other diseases or risk factors for potential malfunction of an organ*	The following information helps in assessing the side effects of these diseases: duration, treatment, quality of treatment. Co-existing laboratory data are also helpful. Previous diseases or surgery hint at potential disease-transmission risks (infection, malignancy, etc.) as well as posing the risk of acquiring nosocomial infections (due to hospital or nursing home admission). This includes considerations about diseases originating from neuro-degeneration, intoxication, auto-immune – or congenital – or inherited disorders as well as unknown aetiology.	Chapters 7, 8, 9, 10
History of recent immunisation	Transmitting live vaccines from the donor into a recipient.	§8.2.4

Abbreviations

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Travel history or residence abroad/overseas, living conditions, social contacts, job description, immigration, private hobbies, pets, contact with fauna, especially bites from pets, domestic or wild animals, birds etc.	This should be evaluated to rule out the risk of tropical or endemic infections. Information on potential exposure to foreign diseases will guide individual decisions as to what additional and specific testing is required. In most countries there are only a few institutions dealing with testing of tropical or other rare diseases (often without a 24/7 service). Timely requests for these additional tests are necessary. The history of travel or residence abroad should include information about living conditions, migration background, refugee status and work places (e.g. sewage plant, woodlands, farm, airport, hospital, foreign countries). This may help to identify risks related to places/countries with inferior hygienic standards or a high prevalence of certain infections. Information about hobbies (e.g. home, garden, animals, woodlands) should be obtained with the same intention.	Chapter 8
Risk of transmitting prion disease	This includes diagnosis or high suspicion of any transmissible spongiform encephalopathy in the donor, a family history of Creutzfeldt–Jakob Disease, and whether the donor was a recipient of human pituitary-gland-derived hormones, *dura mater* or corneal/scleral transplants.	§8.8
Medications before hospital admission (long-term use)	Chronic medication may be harmful to organs and cause damage or it may have been applied to repair damage caused by some kind of organ failure. This consideration also applies to any previous medical treatment, exposure to chemical substances/radiation or immunosuppression.	Chapter 7 as well as chapters 8, 9, 10
Uniform donor health questionnaire	This questionnaire is a complementary checklist that can help to avoid missing important topics.	appendices 10, 11, 12, 13

4. Haemodynamic parameters and further monitoring

Data	Comment, informative value and background	Cross-ref.
Body temperature	Decreased body temperature is common in DBD. Correct diagnosis of brain death requires body temperature > 33 °C, and very low body temperatures may require specific consideration of pathophysiologic derangements (e.g. drowning accidents in cold water). Sometimes, fever may occur due to SIRS and/or infection. In such cases, the taking of cultures may be considered for exclusion of bacterial infections.	Chapters 3, 5, 7 and 8
Heart rate	After failure of vagal stimulation in DBD, the autonomous sinus node of the heart takes over (at a wide range, tachycardia of about 100/min in adults). Arrhythmias occur during or shortly after brain-stem coning.	Chapter 5
Arterial blood pressure	Surrogate for quality of organ perfusion; to be considered in association with demand for vasopressors and diuresis. Consider age adjustment and the need for elevated organ perfusion pressure in cases of pre-existing arterial hypertension without proper treatment.	Chapter 5
Diuresis in last 24 h – with review of last 72 h. Diuresis in last hour	Indicates quality of kidney function if donor is haemodynamically stable and if appropriate fluid balance exists. Polyuria may be due to diabetes insipidus, elevated serum glucose or recovery from acute kidney injury. Oligo-anuria may occur due to haemodynamic instability, volume depletion or acute kidney injury.	Chapters 5 and 7
Central venous pressure	Correction for PEEP is mandatory. It is a questionable surrogate marker for venous filling and right cardiac function. In cases of maintenance problems, invasive monitoring is more informative (PICCO® or similar monitor, echocardiography, a pulmonary artery catheter).	Chapter 5
Pulmonary artery pressure	Can be estimated via echocardiography when no invasive measurement is available.	Chapter 5
Physical and clinical data†	Data from clinical examinations – which are necessary for evaluation of physiological maintenance of the potential donor as well as evaluation of any finding that reveals conditions that remained undetected during interrogation of the donor's medical history – might affect considerations about the suitability of organs for transplantation or risk of disease transmission. Findings at laparotomy and thoracotomy during and after procurement should also be noted. It is important to check for scars from previous surgery in order to identify any missed previous therapy for oncologic reasons, including tattoo marks from previous radiotherapy.	§6.2.2, §6.4 and §6.5

Abbreviations

Anti-HBc: hepatitis B core antibody. BAL: broncho-alveolar lavage. CMV: *Cytomegalovirus*. CPR: cardio-pulmonary resuscitation. DCD: donation after circulatory death. D/R: donor/recipient. EBV: Epstein–Barr virus. HbA1c: haemoglobin A1c. HBsAg: hepatitis B surface antigen. HBV: hepatitis B virus. HCV: hepatitis C virus. HIV: human immunodeficiency virus. HLA: human leukocyte antigen. ICU: intensive care unit. NAT: nucleic acid testing. PEEP: positive end-expiratory pressure. SIRS: systemic inflammatory response syndrome. TPHA: *Treponema pallidum* haemagglutination.

5. Medication during current stay at ICU (for any medication, the timeline and dose should be known)		
Data	**Comment, informative value and background**	**Cross-ref.**
Adrenaline, noradrenaline, dopamine, dobutamine, vasopressin, other vasopressor or inotropic drugs†	Indicative for the kind of haemodynamic status achieved (dose over the timeline is of interest in terms of haemodynamic parameters). Medications used during cardiac resuscitation should be documented separately.	Chapter 5
Blood transfusions†	Erythrocyte concentrate, fresh frozen plasma and thrombocyte concentrate. Units over timeline to be viewed in the context of haemodynamic parameters, coagulation and bleeding disorders. CMV status of the blood products used can be helpful for interpreting the result of CMV screening; but this is a sophisticated procedure and cannot always be provided.	Chapter 5 For CMV, see §8.6.2.6
Plasma expanders†	Type, dose and duration of substitute may be informative about haemodynamic stabilisation or damage to kidneys.	Chapter 5
Other blood products†	Medication for correction of coagulation status.	Chapter 5
Antibiotics†	Indication, type and duration of anti-bacterial, anti-fungal or anti-viral medication and success in treatment of infections. Treatment according to resistance patterns should be confirmed.	Chapter 8
Anti-diuretics†	Treatment of diabetes insipidus (context of diuresis and serum-sodium level).	Chapter 5
Diuretics†	Requirements for initiating diuresis or correction of fluid balance due to overload should be recorded. Applications should be viewed in context with diuresis and kidney function parameters.	Chapter 5
Insulin†	Glucose metabolism is frequently deranged after admission to ICU.	Chapter 5
Steroids†	Treatment of SIRS.	Chapter 5
Other medication†	Documentation of other relevant medication.	Chapter 5

Ventilation and pulmonary function		
Data	**Comment, informative value and background**	**Cross-ref.**
Respirator settings, blood gas analysis	Conclusive for protective ventilation and achieved gas exchange. Standardised interpretation of blood gas analysis for lung donation includes the following procedure: (1) Suction the airway, (2) Perform lung recruitment, (3) Ventilate at PEEP ≥ 5 cm H_2O at FiO_2 = 1.0 for 10 minutes. Clinical diagnosis of brain death by an apnoea-test is often strictly regulated and requires specific ventilator settings and normal $paCO_2$.	Chapter 7
Chest X-ray (thoracic-CT), bronchoscopy, BAL	To be considered if pulmonary infection is suspected and to assess acute or chronic structural damage to the lung. BAL samples should be sent for microbiological tests.	Chapters 7 and 8

7. Other issues		
Data	**Comment, informative value and background**	**Cross-ref.**
Laboratory parameters,† imaging† and other complementary tests	These data are complementary to the clinical data and explain, clarify and verify them regarding assessment of organ quality and risks of potentially transmissible diseases.	§6.2.3 and §6.2.4

8. Final documentation of success in donor maintenance		
Data	**Comment, informative value and background**	**Cross-ref.**
Haemodynamic	Monitoring and preventing hypotension, hypertension, arrhythmias and cardiac arrest, and maintaining arterial pressure, volume substitution etc., aiming at preserving cardiac output and perfusion of other organs.	Chapter 5
Electrolyte	Monitoring and correcting hypokalaemia, hyperkalaemia, hyponatraemia and hypernatraemia.	Chapter 5
Body temperature	Keep within a physiological range (> 34 °C).	Chapter 5
Endocrine	Monitoring the clinical effects and preventing changes in the hypothalamic-pituitary-thyroid and hypothalamic-pituitary axis (diabetes insipidus) and changes in glucose metabolism.	Chapter 5

Abbreviations

Anti-HBc: hepatitis B core antibody. BAL: broncho-alveolar lavage. CMV: *Cytomegalovirus*. CPR: cardio-pulmonary resuscitation. DCD: donation after circulatory death. D/R: donor/recipient. EBV: Epstein–Barr virus. HbA1c: haemoglobin A1c. HBsAg: hepatitis B surface antigen. HBV: hepatitis B virus. HCV: hepatitis C virus. HIV: human immunodeficiency virus. HLA: human leukocyte antigen. ICU: intensive care unit. NAT: nucleic acid testing. PEEP: positive end-expiratory pressure. SIRS: systemic inflammatory response syndrome. TPHA: *Treponema pallidum* haemagglutination.

Coagulation	Monitoring and correction of major coagulopathies.	Chapter 5

9. Specific data to be provided in cases of uncontrolled DCD		
Data	**Comment, informative value and background**	**Cross-ref.**
Event of cardiac arrest leading to unsuccessful resuscitation, determination of death and procurement of organs with proper preservation	It is imperative to provide all data available *ante mortem* and before the event of cardiac arrest. Of special interest are: the particular time when last seen alive, start of CPR by both non-professionals and professionals, including details of CPR, arrival in hospital, end of CPR, start and end of no-touch period, cannulation, preservation and procurement.	Chapter 12

10. Specific data to be provided in cases of controlled DCD		
Data	**Comment, informative value and background**	**Cross-ref.**
Detailed description of agonal period starting from the moment where full life-sustaining therapy is discontinued until determination of death and recovery of organs with proper preservation	It is imperative to provide all data available *ante mortem* and before the event of terminating life-sustaining therapy. In a few countries, donation after euthanasia is allowed. Then the same principles apply. Of special interest are: the particular time of withdrawal of therapy, type and duration of agonal period, terminal cardiac arrest, start and end of no-touch period, cannulation, preservation and procurement.	Chapter 12

Abbreviations

Anti-HBc: hepatitis B core antibody. BAL: broncho-alveolar lavage. CMV: *Cytomegalovirus*. CPR: cardio-pulmonary resuscitation. DCD: donation after circulatory death. D/R: donor/recipient. EBV: Epstein–Barr virus. HbA1c: haemoglobin A1c. HBsAg: hepatitis B surface antigen. HBV: hepatitis B virus. HCV: hepatitis C virus. HIV: human immunodeficiency virus. HLA: human leukocyte antigen. ICU: intensive care unit. NAT: nucleic acid testing. PEEP: positive end-expiratory pressure. SIRS: systemic inflammatory response syndrome. TPHA: *Treponema pallidum* haemagglutination.

Table 6.5. **General conditions in the donor that are risk factors for an unsuccessful transplantation**

Condition	**Conditions that might be limiting for successful donation**	**Cross-reference**
General	***Unfavourable – but avoidable and reversible*** Avoidable are complications in management of a patient *ante mortem* or potential donor *post mortem* by proper intensive care and donor management. Recovery from initial periods of shock, resuscitation or complications during intervention can be monitored; while we know that severe cerebral lesions cause indirect damage to organs, especially without proper neuro-critical care. ***Irreversible*** Acute multiple organ failure without possibility of recovery or chronic organ failure with structural damage both require a case-by-case decision.	Chapter 5 and Chapter 7
Infection	Decisions on a case-by-case basis: Systemic bacterial infections: 48 h definitively effective antibiotic therapies are considered to be sufficient for inclusion of a donor (negative culture preferred). Existing local infections or colonisations do not exclude donation of other organs (e.g. pneumonia, urinary tract infection). Fungus, virus, parasites: caution if the pathogen is detected in the blood. These infections must be cured or, after a case-by-case decision, selected recipients may have an organ transplanted because either treatment is available or recipient-related infection requires mandatory treatment anyway. CMV, EBV, toxoplasmosis etc: consider chemoprophylaxis in the recipient if D^+/R^-. Acute donor infections with spread of the pathogen into the blood (e.g. confirmed by NAT): such conditions require case-by-case decisions after consulting a transplant infectious disease expert for final conclusions. Antibodies detected against a pathogen can document only that the immune system has responded to the pathogen. Reactive IgM antibodies do not clarify whether the pathogen has spread to the bloodstream or not.	Chapter 8
	Special consideration should be given to exclusion of asymptomatic infection by HIV, HBV, HCV, HTLV I/II virus, *Trypanosoma cruzi* and other pathogens in donors who originate from endemic areas for these infections or populations with increased risk for window-period infections or vertical transmission.	§8.2
Malignancies	Decisions on a case-by-case basis.	Chapter 9

Poisoning	For appropriate determination of brain death, excluding poisoning is mandatory. After detoxification and/or recovery from poisoning, each organ should be individually evaluated.	Chapter 10
Inherited or rare diseases	Decisions on a case-by-case basis: systematic reports are not available. Further information can be retrieved from the emergency guidelines at www.orpha.net for very rare diseases. Systemic diseases with possible effects on graft quality (e.g. collagen disease or systemic vasculitis, or metabolic disorders such as maple syrup disease, oxalosis etc.) require additional examinations.	Chapter 10
Age-related co-morbidities	Co-morbidities in donors are very common. Decisions must be made on a case-to-case basis. With advanced age there is an increased frequency of arterial hypertension, diabetes and obesity, and of the side effects of chronic alcohol abuse and smoking. Beyond cardiovascular risks, including progressive arteriosclerosis, irreversible organ damage may occur. In contrast, properly treated arterial hypertension and/or diabetes and a lifestyle including enough physical activity may compensate for or limit such changes. Therefore, in the advanced-age donor population (e.g. > 60 years), significant differences exist in the suitability of each individual organ for transplantation. This issue requires assessment of 'biological age' instead of 'chronological age'.	Chapter 7

Abbreviations
CMV: *Cytomegalovirus*. DCD: donation after circulatory death. D/R: donor/recipient. EBV: Epstein–Barr virus. HBV: hepatitis B virus. HCV: hepatitis C virus. HIV: human immunodeficiency virus. HTLV: human T-lymphotropic virus. NAT: nucleic acid test.
Cross-reference: Refer to the chapter or section (§) outlined for all details to be considered.

6.4. Examination during procurement

Prior to the procurement of any graft from a donor, a detailed macroscopic examination should be performed and documented (see Chapter 11). It is the responsibility of the surgeon who is performing the procurement to document any anomalous anatomical findings or suspicious pathological findings. During procurement, the entire abdominal and thoracic cavities must be inspected for any suspicious lesion in every donor.

Systemic diseases with possible effects on organs to be transplanted (e.g. collagen disease or systemic vasculitis) may require additional examination. The final decision to use grafts also depends on macroscopic evaluation by the procuring surgeon and, if necessary, histology of an organ biopsy.

In cases of abnormal findings, further investigations should be made and the results must be included in the donor documentation. For example, any space-occupying lesion detected either during pre-procurement investigations or during procurement should be verified by histopathologic examination of the whole lesion, or samples from a suspected area of contamination should be sent for microbiologic examination (swab, fluids etc.). Any abnormal findings must, without delay, be clearly communicated to the transplantation units receiving organs from the donor. When applicable, the formal requirements for traceability in the EU directive 2010/53 should be observed.

In cases of donors with previous history of malignancy, a plan should be formulated in advance as to how any space-occupying lesion detected incidentally would be examined and what consequences might result from the use of any organ procured.

6.5. Examinations after procurement

Performing an autopsy after procurement, for final exclusion of undetected diseases, can be helpful. However, experience shows that obtaining permission for an autopsy can be more difficult than obtaining permission for donation, unless medical evidence exists that may persuade donor relatives to insist on an autopsy. Therefore it is mandatory to carry out a thorough inspection at procurement (see §6.2).

Any investigation initiated before or during procurement with pending final result must be integrated into the final donor characterisation (e.g. a frozen section of a space-occupying lesion will have to be followed by paraffin embedding). The results must be forwarded immediately to all relevant institutions (e.g. OPO, transplant centres, tissue establishment). These results might change the final conclusions of donor characterisation and they might cause the reporting of a serious adverse event in order to prevent further harm to other potential recipients (see Chapter 16). When applicable, the formal requirements for traceability in the EU directive 2010/53 should be observed.

In cases where results are pending, grafts can be offered to those centres and recipients who are willing to accept the risks associated with unknown data. Indeed, the transplant team might assess the

risks posed by non-transplantation as outweighing the risks associated with incomplete data, and might choose to monitor the situation before and when results become available.

Whenever a procured graft is finally not transplanted, then it is best practice to perform histopathologic examination to exclude other undetected disease and to confirm the appropriateness of the decision to not transplant the graft.

Donor and organ characterisation is a continuous process, and data collected before, during and after the procurement should be complemented by other results (for example, lab tests) as soon as they become available. Communication between the donor co-ordinator, OPO and the different transplant centres involved, as well as between the transplant centres themselves, is vital, and is also critical in the case of cross-border organ exchange. The correct definition of these communication channels and their availability to medical teams are essential for traceability and vigilance purposes within well-established donation and transplantation systems.

Follow-up studies of all grafts transplanted are also recommended for vigilance purposes and for quality assurance of the donor characterisation process.

The principles summarised in this chapter are confirmed by the European Foedus project [41], which is evaluating the practice of donor and organ characterisation to establish the best data set needed for efficient organ exchange across the borders of the various European organ-exchange organisations. As a major additional benefit, this project provides valuable information on how we can collect data on donor evaluation for future analysis of donor characteristics in Europe.

6.6. Examinations required for optimising organ allocation and recipient protection from avoidable immunological complications

Examinations like HLA-typing or ABO blood group determination and anthropometric or demographic data do not characterise the donor or organ quality itself. They are implemented in order to allocate a particular graft to the recipient with the greatest benefit of transplantation, as well as to rule out serious avoidable complications (e.g. antibody-mediated rejection in kidney transplantation). These data are collected as part of the donor and organ characterisation, but their purpose is to benefit the recipient regarding outcome as well as the purpose of organ allocation. In order to avoid unnecessary delays after procurement (see Chapter 11), it must be carefully considered which investigations can be performed during the time interval that starts with declaration of death and final consent and continues until the start of procurement and cross-clamp.

It is important that the extent of recipient immunisation against HLA or histocompatibility epitopes of the donor is properly identified. Proper prospective HLA-typing of the donor by molecular-biologic methods – i.e. polymerase chain reaction (PCR-SSO or PCR-SSP) in low and/or high resolution as indicative of at least HLA-A*, -B*, -C*, -DRB1*, -DQB1*, -DQA1*, -DPA1*, -DPB1*, -DRB3*, -DRB4*, -DRB5* alleles (equivalent to serologic antigens of HLA-A, -B, -C, -DR, -DQ, -DP) enables transplant centres to perform virtual cross-match and further compatibility evaluation without risk of unnecessary organ loss. For example, such investigations help to reduce the risk of graft loss in the long term due to existing or newly developing donor-specific antibodies; this risk is not only relevant in sensitised kidney recipients [42-43].

Since there are ongoing changes in the established methods of improving quality in terms of outcome, it is recommended to consider adoption of new technologies in the light of the most recent changes. Currently high-resolution HLA-typing is limited to specialised facilities and/or conditions where prolonged turnaround times are acceptable. Technologies need to be developed that overcome the limitations of low resolution. Up to now the needs of HLA-typing have not been well defined, especially

1. what new technology is needed for:
   - improving allocation,
   - virtual crossmatching,
   - crossmatch testing,

2. what further investigations are needed to minimise immunological risks related to:
   - issues compromising long-term outcome,
   - actual daily practice.

For all organs procured from deceased donors, it is usually preferred to transplant them into ABO-blood group-compatible recipients. In specialised centres ABO-incompatible transplants are performed using approved protocols [44]. By contrast, in living donor transplantation (e.g. kidneys), ABO-incompatible transplantation is a relatively safe and successful procedure in properly pre-treated/desensitised recipients, although an increased risk has been observed regarding infectious complications in

the recipient due to intensified immunosuppression [45-47].

6.7. Appropriate amount of evaluation

For the characterisation and assessment of the donor as well as the organ, an appropriate amount of investigation is necessary as indicated. The correct balance must be found between examinations performed and not performed. Over-evaluation is frequently a symptom of defensive medicine. This ties down a lot of resources – not only in money – and it creates a lot of results, which may be confusing or difficult to interpret and therefore may lead to rejection of a potentially suitable organ donor or grafts. Under-evaluation of the donor, on the other hand, may lead to overlooking a clinically relevant situation that may harm the recipient by transmission of a disease or by transplantation of a damaged organ. Both situations are harmful for the future patient.

For example, the varying incidence of different tumours in different age groups should be taken into consideration. In addition, the incidence of coronary artery disease (CAD) is extremely low in people in the age range 20 to 30 years compared to those in the age range of 50 to 60 years. This does not exclude CAD in younger people, but it is very unlikely. Thus excessive diagnostics would be harmful when balancing the benefit of increased knowledge obtained by coronary artery angiography *versus* the associated complications. But in elderly people it might be justified to perform such diagnostics, especially if risk factors for cardiovascular co-morbidities exist. Still this picture might change when we have the risk factor of insulin-dependent diabetes mellitus or exposure to certain immunosuppressive drugs in a former kidney graft recipient at a younger age. Such situations require an individualised indication of the need for a particular special examination, which will not be covered well by strict adherence to protocols without assessing each case individually.

6.8. Formal issues and documentation

Among the member states of the Council of Europe, regulations on transplantation and the required documentation vary. Transplantation teams must follow national and/or regional laws. The rest of this section concerns European Union legislation.

According to Directive 2010/53/EU on standards of quality and safety of human organs intended for transplantation, Article 7 ('organ and donor characterisation'), EU member states shall ensure that all procured organs and the donors thereof are characterised before transplantation, through collection of the information set out in the Annex to the Directive. Part A of the Annex contains a set of minimum data that must be collected for each donation. Part B of the Annex contains a set of complementary data to be collected in addition, based on a decision of the medical team, taking into account the availability of such information and the particular circumstances of the case. If, according to a risk–benefit analysis in a particular case, including in life-threatening emergencies, the expected benefits for the recipient outweigh the risks posed by incomplete data, an organ may be considered for transplantation even where not all of the minimum data specified in Part A of the Annex are available. It should be added that, while the EU directive mandates common quality and safety standards, it does not prevent any EU member state from maintaining or introducing more stringent rules, including rules on organ and donor characterisation.

A database of donor information should be maintained that protects anonymity. Directive 2010/53/EU states in its Article 16 that "Member States shall ensure that the fundamental right to protection of personal data is fully and effectively protected in all organ donation and transplantation activities". All necessary measures must be taken to ensure that "the data processed are kept confidential and secure" and "donors and recipients whose data are processed … are not identifiable …. Any unauthorised accessing of data or systems that makes identification of donor or recipients possible shall be penalised".

Donor and recipient confidentiality should be maintained throughout the entire process. But, for medical purposes such as traceability and vigilance, data concerning the organ donor procedure must be documented on standardised forms. The forms outlined in sections 6.8.1 and 6.8.2 should exist for every donor and organ. Directive 2010/53/EU also prescribes that "Member States shall ensure that data required for full traceability is kept for a minimum of 30 years after donation. Such data may be stored in electronic form". Indeed, it must be ensured that all organs procured, allocated and transplanted can be traced from the donor to the recipient and vice versa in order to safeguard the health of (living) donors and recipients (also in the case of international organ exchange). EU Directive 2010/53 also sets out requirements for a system for reporting of serious adverse events (SAEs) and reactions (SARs) that occur in relation to organ donation (Chapter 16).

6.8.1. Donor Report

The donor report or 'donor information form' should contain all relevant information about the donor to allow evaluation of eligibility for organ donation and to support the allocation process (examples used in the Eurotransplant area and Foedus project [48] are shown in Appendix 13). The person who refers the donor from the referring hospital to the OPO or organ exchange organisation should complete the form, either as electronic or written document. The form should accompany the organs and be maintained in the donor file. It should be archived separately from recipient notes. In practice, for donors, this information should be maintained in the donor records of the OPO. The donor records should include the donor information form and the documents proposed in chapters 6 and 7, as well as the records allowing reproducibility of consent/authorisations and death certificates. The death certificate must not be in paper form when an appropriate electronic database exists.

Exchanging donor data between different institutions involved in the donation/transplantation process must be done with care: errors can occur as a result of clerical issues, transcription problems (e.g. the interface used to transfer data from paper forms to IT systems) or limited human resources involved in the process. Such errors can cause avoidable serious adverse events or reactions (Chapter 16). Therefore it is recommended that critical data such as blood group or virological tests are reviewed with special care, for example face to face by two independent persons with reference to the original files and data exchanged electronically at key points. Verbal communication of key data only, without visual verification of the original files by both parties, is not optimal and should be discouraged.

6.8.2. Organ report

This form should contain all data on donor organs at the time of procurement (see Chapter 11; see also Appendix 13).

6.8.3. Donor sample archive

Samples of relevant donor material (e.g. serum, remains from HLA-typing) should be stored for retrospective studies, if indicated, for a period of 10 years (see chapters 11, 15 and 16).

6.9. Conclusion

Primarily, donor characterisation contributes to the safety and quality of organs. Risk evaluation of donor and recipient factors has to be carried out on an individual, case-by-case basis regarding the issues associated to a donor in general. In addition, the organ-specific selection criteria must be considered in this process. There may be factors that make a given donor absolutely unsuitable for a specific recipient, whereas the same donor could provide a life-saving graft for another recipient. This is why there are almost no absolute contraindications against organ donation. Therefore all details outlined in Chapter 7 have to be taken into account before a decision can be made on whether to continue or not to continue with the donation process. Because organ donation procedures in DBD or DCD are carried out within some time constraints, donor characterisation can never cover all possible aspects but needs to be carefully planned and structured.

Research agenda

From the literature and discussion of the available evidence, several topics have been identified for which evidence is inconsistent, insufficient or non-existent. The authors of this guide recommend that future research, where possible in well-designed randomised clinical trials, should focus on the following research gaps:

1 Significant overlay to questions of Chapter 7.
2 Proof of concept of the process about its appropriateness.

6.10. References

1. Alliance-O (European Group for Co-ordination of National Research Programmes on Organ Donation and Transplantation), available at http://ec.europa.eu/research/fp7/pdf/era-net/fact_sheets/fp6/alliance-o_en.pdf, accessed 15 May 2021.
2. Project Dopki (Improving knowledge and practices in organ donation), available at www.ont.es/internacional/Documents/dopki.pdf, accessed 15 May 2021.
3. Nanni Costa A, Grossi P, Gianelli Castiglione A *et al.* Quality and safety in the Italian donor evaluation process. *Transplantation* 2008;85:S52-S56.
4. Feng S, Goodrich NP, Bragg-Gresham JL *et al.* Characteristics associated with liver graft failure: the concept of a donor risk index. *Am J Transplant* 2006; 6:783-90.
5. Rao PS, Schaubel DE, Guidinger MK *et al.* A comprehensive risk quantification score for deceased donor

kidneys: the kidney donor risk index. *Transplantation* 2009;88:231-6.

6. Frühauf NR, Fischer-Fröhlich CL, Kutschmann M *et al.* Joint impact of donor and recipient parameters on the outcome of liver transplantation in Germany. *Transplantation* 2011;92:1378-84.
7. Giessing M. Ten years of the Eurotransplant senior program: are there still age limits for kidney transplantation? *Urologe* A 2009;48:1429-37.
8. Giessing M, Fuller TF, Friedersdorff F *et al.* Outcomes of transplanting deceased-donor kidneys between elderly donors and recipients. *J Am Soc Nephrol* 2009; 20:37-40.
9. Andrés A, Fischer-Fröhlich CL. Chapter 4: Organ Viability: 99-154. In: Valero R, ed. *Transplant coordination manual*. 3rd edition. Barcelona: Aguilógrafic, 2014. ISBN: 978-84-616-8840-1.
10. Fischer-Fröhlich CL, Königsrainer A, Nadalin S. Spenderselektion und neues Transplantationsgesetz. *Allgemein- und Viszeralchirurgie up2date* 2012;5: 339-56.
11. Axelrod DA, Sung RS, Meyer KH *et al.* Systematic evaluation of pancreas allograft quality, outcomes and geographic variation in utilization. *Am J Transplant* 2010;10:837-45.
12. Echterdiek F, Schwenger V, Döhler B *et al.* Kidneys from elderly deceased donors – is 70 the new 60? *Front Immunol* 2019;10:2701. https://doi.org/10.3389/fimmun.2019.02701). Add on information see also CTS Transplant Newsletter 1/2020 on www.ctstransplant.org, accessed 15 May 2021.
13. Thompson I, Rosales B, Kelly P *et al.* Epidemiology and comorbidity burden of organ donor referrals in Australia: cohort study 2010-2015. *Transpl Direct* 2019;5:e504; https://doi.org/10.1097/TXD.0000000000000938.
14. Council of Europe. *Guide to the quality and safety of tissues and cells for human application*. 5th edition. Strasbourg: Council of Europe, 2022.
15. Council of Europe. *Guide to the quality and safety of organs for transplantation*. 7th edition. Strasbourg: Council of Europe, 2018.
16. Council of Europe and Organización Nacional de Trasplantes. *Newsletter Transplant*: International figures on donation and transplantation 2019. European Directorate for the Quality of Medicines & HealthCare of the Council of Europe (EDQM), 2020, Strasbourg, France available at https://freepub.edqm.eu/publications/NT-archive/detail, accessed 11 April 2022.
17. Port FK, Bragg-Gresham JL, Metzger RA *et al.* Donor characteristics associated with reduced graft survival: an approach to expanding the pool of kidney donors. *Transplantation* 2002;74:1281-6.
18. Silberhumer GR, Rahmel A, Karam V *et al.* The difficulty in defining extended donor criteria for liver grafts: the Eurotransplant experience. *Transpl Int* 2013;26:990-8. https://doi.org/10.1111/tri.12156.
19. Maglione M, Ploeg RJ, Friend PJ. Review: donor risk factors, retrieval technique, preservation and ischemia reperfusion injury in pancreas transplantation. *Curr Opin Organ Transplant* 2013;18:83-8.
20. Thierry B, Kandaswamy R. Invited commentary: who needs a pancreas donor risk index? *Transpl Int* 2015; 28:1025-7.
21. Lledó-Garciá E, Riera L, Passas J *et al.* Spanish consensus document for acceptance and rejection of kidneys from expanded criteria donors. *Clin Transplant*, 2014;28:1155-66.
22. Wang J, Skeans M, Israni A. Current status of kidney transplant outcomes: dying to survive. *Adv Chronic Kidney Dis* 2016;23:281-6.
23. Eurotransplant Foundation: *Eurotransplant manual*, Chapter 5: ET-liver allocation system (ELAS). Section 5.3.2 Enis Donor profile. Leiden: Eurotransplant Foundation, 2020, available at www.eurotransplant.org/professionals/eurotransplant-manual/, accessed 15 May 2021.
24. Blok JJ, Braat AE, Adam R *et al.* Validation of the donor risk index in orthotopic liver transplantation within the Eurotransplant region. *Liver Transpl* 2012; 18(1):112-19.
25. Collett P, Friend P, Watson C. Factors associated with short- and long-term liver graft survival in the United Kingdom: development of a UK donor liver index. *Transplantation* 2017;101:786-92.
26. Pascual J, Pérez-Saéz MJ. Kidney profile index: Can it be extrapolated to our environment? *Nefrologia* 2016; 36:465-8.
27. Gupta A, Francos G, Frank A, Shah A. KDPI score is a strong predictor of future graft function: Moderate KDPI (35 - 85) and high KDPI (> 85) grafts yield similar graft function and survival. *Clin Nephrol* 2016;86: 175-182.
28. Braat AE, Blok JJ, Putter H *et al.*, European Liver and Intestine Transplant Association (ELITA) and Eurotransplant Liver Intestine Advisory Committee (ELIAC). The Eurotransplant donor risk index in liver transplantation: ET-DRI. *Am J Transplant* 2012;12(10): 2789-99.
29. Blok JJ, Putter H, Rogiers X *et al.* Combined effect of donor and recipient risk on outcome after liver transplantation: research of the Eurotransplant database. *Liver Transpl* 2015;21:1486-93.
30. Reichert B, Kaltenborn A, Goldis A, Schrem H. Prognostic limitation of the Eurotransplant donor risk index in liver transplantation. *Journal of*

Negative Results in Biomedicine 2013;12:18. https://doi.org/10.1186/1477-5751-12-18.

31. Tanriover B, Mohan S, Cohen DJ *et al.* Kidneys at higher discard: expanding the role of dual kidney transplantation. *Am J Transpl* 2014;14:404-15.
32. Blok JJ, Kopp WH, Verhagen MJ *et al.* The value of PDRI and P-PASS as predictors of outcome after pancreas transplantation in a large European pancreas transplantation center. *Pancreas* 2016;45(3):331-6.
33. Mittal S, Lee F, Bradbury L *et al.* Validation of the pancreas donor risk index for use in a UK population. *Transpl Int* 2015;28(9):1028-33.
34. Winter A, Féray C, Audureaun E *et al.* External validation of the donor risk index and the Eurotransplant donor risk index on the French liver transplantation registry. *Liver Int* 2017 [epub ahead: February 2017, https://doi.org/10.1111/liv.13378:1-10].
35. Rege A, Irish B, Castleberry A *et al.* Trends in usage and outcomes for expanded criteria donor kidney transplantation in the United States characterized by kidney donor profile index. *Cureus* 2016 Nov 22;8(11): e887.
36. Li J, Kaiser G, Schaffer R *et al.* Inaccurate estimation of donor body weight, height and consequent assessment of body mass index may affect allocation of liver grafts from deceased donors. *Transpl Int* 2009;22:356-7.
37. Holloway J, Ranse K, Currie M *et al.* An integrative review of the physical examination performed on deceased potential organ and tissue donors. *Progress in Transplantation* 2019;29:84-94.
38. CKD Work Group. Kidney disease: improving global outcomes. KDIGO 2012 Clinical practice guideline for the evaluation and management of chronic kidney disease. *Kidney Inter* 2013;3(Suppl):1-150.
39. Mensink J, Pol R, Nijboer W *et al.* Whole body CT imaging in deceased donor screening for malignancies. *Transplantation Direct* 2019;5:e508 https://doi.org/10.1097/TXD.0000000000000953.
40. Ghorbani F, Najafizadeh K, Fischer-Fröhlich CL, Mojtabaee M. Impact of recruitment maneuvers to cover adverse effects of donor transfer. *Experimental and Clinical Transplantation* 2019;18(4):429-35. https://doi.org/10.6002/ect.2019.0236.
41. Kaul DR, Covington S, Taranto S *et al.* Solid organ transplant donors with central nervous system infection. *Transplantation* 2014;98:666-70. https://doi.org/10.1097/TP.0000000000000117.
42. Abramowicz D, Cochat P, Claas F *et al.* European renal best practice guideline in kidney donor and recipient evaluation and perioperative care. *Nephrol Dial Transplant* 2013;28:ii1–ii71.
43. Tait B, Süsal C, Gebel H *et al.* Consensus guidelines on the testing and clinical management issues associated with HLA and non-HLA-antibodies in transplantation. *Transplantation* 2013;85:19-47.
44. Schukfeh N, Lenz V, Metzelder ML *et al.* First case studies of successful ABO-incompatible living-related liver transplantation in infants in Germany. *Eur J Pediatr Surg* 2015 Feb;25(1):77-81. https://doi.org/10.1055/s-0034-1387936 [epub 2015 Jan 2].
45. Shin M, Kim SJ. ABO incompatible kidney transplantation – current status and uncertainties. *J Transplant* 2011;970421. https://doi.org/10.1155/2011/970421.
46. Scurt F, Ewert L, Mertens PR *et al.* Clinical outcomes after ABO-incompatible renal transplantation: a systematic review and meta-analysis. *Lancet* 2019;393: 2059-72.
47. Speer C, Kälble F, Nusshag C *et al.* Outcomes and complications following ABo incompatible kidney transplantation performed after desensitization by semi-elective immunoadsorption – a retrospective study. *Transpl Int* 2019;32:1286-96.
48. Foedus (Facilitating Exchange of Organs Donated in EU member states, EU-funded project), project website: www.foedus-eoeo.eu/#/public, accessed 16 May 2021.

Related material

Appendix 10. Rationale document for medical and social history questionnaire (United Kingdom)
Appendix 11. Donor patient history questionnaire (Germany, English-language version)
Appendix 12. Physical examination of an organ or tissue donor (Dutch Transplant Foundation)
Appendix 13. Donor and organ information forms
Appendix 14. Donor examination by various means
Appendix 15. Grading for biopsies at histopathological examinations (English-language version)

Chapter 7. Specific organ characterisation, assessment and selection criteria

7.1. Introduction

Organ-specific assessment supports the decision about which organs of a donor can be transplanted without unnecessary harm to a recipient but with appropriate function to support survival. Theoretically this occurs after the general assessment of the donor has been performed, as outlined in Chapter 6, though for pragmatic reasons there is an overlay of the two processes in order to save resources. The summary of all data obtained during general donor and specific organ characterisation allows a prediction of whether transplantation of a particular graft will be beneficial to the patient or not. Only after this risk–benefit assessment is completed should transplantation of a particular organ into a particular recipient be considered, acknowledging the limitations of predicting the outcomes after transplantation (see Chapter 18).

The health status of patients on the waiting list during the waiting period most often deteriorates continuously. The individual urgency for transplantation of a recipient correlates with the risk of not surviving on the waiting list. For this reason, the threshold for acceptance of risks related to an organ will vary for each patient according to their situation at that time.

The specific selection criteria for organs for transplantation have changed and will continually be changing according to the current state of knowledge and the condition of the potential recipients on the waiting lists. Therefore, it is essential to continuously monitor the health status of wait-listed patients and to remove patients from the list if they are no longer transplantable. Equally, the acceptance criteria stored in the records for organ-exchange issues must be updated properly.

Importantly, the assessment, selection and allocation of organs must always be done relative to the needs and status of the patients waiting for transplantation at that specific time point. Sometimes, an organ that can be urgently needed, and at that moment lifesaving for one specific patient, could be highly unsuitable or even harmful for another patient. From the viewpoint of the donor's co-morbidity and perceived risks, such considerations require close collaboration by the intensive care unit, organ procurement organisation, organ allocation organisation and recipient centres. The formal structure is different in each country.

Currently the majority of organs are recovered from donors whose death has been determined by neurologic criteria – donation after brain death (DBD). Selection criteria for DBD donors are reviewed here. For donation after circulatory death (DCD), some additional specific criteria are summarised in Chapter 12. Specific and additional criteria for living donors are outlined in Chapter 13. For the specific selection criteria for tissue or cell donation, please refer to the latest edition of the Council of Europe *Guide to the quality and safety of tissues and cells for human application*.

The four major categories of risk factor limiting

the outcomes of transplantation are summarised in sections 6.1.1 (Risk assessment of general donor – not receiving an organ in time), 6.1.2 (Risk assessment of general donor – disease-transmission risks), 6.1.3 (Risk assessment of the likelihood of failure associated with a specific graft) and 6.1.4 (Risks not associated with the donor or the graft donated).

Organ-specific diagnostic and selection criteria are reviewed in this chapter in this order: kidney, liver, pancreas, intestine, heart and lung. For vascularised composite allografts (VCAs) please refer to Chapter 15. Although undertaken for a specific organ, many investigations are useful in providing information about multiple organs.

In the future, organ assessment and selection processes may change due to the introduction of new organ-preservation methods, by which organ quality may be improved and could be assessed during preservation time (see Chapter 11). Since cold storage is still the most frequent method used for organ preservation, the considerations about assessment and selection are based on this technology. This viewpoint will have to be revised in upcoming editions of this guide as knowledge about the role and benefits of machine preservation methods increases.

7.2. Organ-specific assessment and selection criteria

Acceptance criteria for organs are mainly based on an assessment of the function and morphology of the donor organ. These criteria may vary between transplant teams and may also depend on recipient characteristics as well as the current waiting-list situation.

Theoretically, if organ preservation and the surgical techniques of procurement and transplantation have been appropriate, any organ functioning well in a donor should function after implantation in the recipient. Sometimes grafts fail to recover their function, and delayed graft function (DGF) or primary non-function (PNF) may occur. The first priority of organ-specific selection criteria and donor management is to minimise DGF or PNF, although these events are not always donor-related. The second priority is to avoid transplantation of a damaged organ, which may lead to long-term harm. Daily clinical practice demonstrates that many transplanted grafts function well even though they did not fulfil the published selection criteria [1]. Therefore, organ viability criteria must be continually adjusted, based on state-of-the-art medical practice and changes within the population constituting the current donor pool. Such an adjustment is not easy to perform because large randomised studies are not available for practical and ethical reasons [1]. To cover this issue the term 'expanded-criteria donor' (ECD) has been introduced in the field, as either a binary or a continuous risk index, as discussed in Chapter 6.

In organs affected by a specific disease, the use of the organ for transplantation must be considered with care: when progression of the disease is unlikely or if estimated duration of graft survival exceeds that of patient survival (see Table 6.3 as guidance for a decision pathway) then transplantation can be considered after informed consent by the recipient [1-4]. In addition, the following issues may apply to any organ and require case-by-case decisions, but none of these issues should be used as an exclusion criterion *per se*:

- Re-use of previously transplanted grafts is possible as outlined in Chapter 10 [1, 5-7].
- The same can be said for previous trauma with possible harm to the donated organs. Here, without inspection during procurement, no final assessment is possible. An exact description of the trauma mechanism is helpful for further decisions, e.g. in a motor vehicle accident a deceleration trauma to the mesenteric root may affect the quality of the pancreas and intestine [8].
- In cases of damage or disease to the central vessels (e.g. aneurysm of the aorta), procurement techniques used in living donation may be considered (e.g. *ex situ* preservation, no aortic patch) instead of not using an organ.

7.2.1. Kidney selection criteria

7.2.1.1. *Issues in kidney selection*

a. *Donor age*

No chronological age limit applies in very young and elderly donors [9-14], although grafts procured from advanced age donors could preferably be used in elderly recipients because the limited duration of graft function (e.g. Eurotransplant Senior Program) may be acceptable based on the limited life expectancy of elderly recipients and their health deterioration while waiting for a kidney transplant [15-19]. In such programmes, matching for histocompatibility is a beneficial side effect [20], while the main challenge is how to manage elderly recipients receiving grafts from elderly donors [21]. Many studies have concluded that increased donor age is associated with an increased risk of graft failure, especially in cases where donor age exceeds 70 years [9, 22-25].

There is a decline in the number of functioning nephrons with increasing age, suggesting that age matching is appropriate [26-27]. According to the Collaborative Transplant Study, in European recipients five-year death-censored graft survival for donors older than 70 years is now (2007-16) equivalent to donors 60-69 years old ten years ago (1997-2006) [28]. In some countries, an age-match between donor and recipient is considered so as to give grafts from young donors to younger recipients, after adjustment for co-factors, to allow longer graft survival [29-31]. Further protocols should exist that avoid the addition of risk factors on top of the age-related limitation of kidney graft function (e.g. prolonged ischaemia times, donor-specific antibodies in the recipient) [32]. In addition, methods for optimised organ preservation and for *ex situ* organ evaluation can be considered in older donors (e.g., machine perfusion of kidneys) [33].

Finally, when discussing the issue of donor age and its impact on inferior graft function rate, we should use as reference point the benchmark of whether the patient has a bigger chance of survival without major complications when receiving an aged graft *versus* remaining on dialysis. For example Arcos *et al.* seem to show that there is a survival benefit when accepting an aged donor graft compared to remaining on dialysis [34].

b. *Past and current medical history*

There should be an evaluation of the medical history (present and past), with special attention to conditions possibly affecting kidney function and quality. Chronic systemic conditions and diseases affecting the kidneys – such as the metabolic syndrome, arterial hypertension and diabetes mellitus, as well as chronic kidney disease and albuminuria (see §7.2.1.1c) are risk factors for inferior outcomes after kidney transplantation, even after adjustment for donor age and quality of care and treatment for the above-mentioned problems [35-38].

Chronic urinary tract infections and other chronic infections might also be important to consider. Reports of previous surgery or interventions involving the kidneys or urinary tract should be studied. Positive urinary cultures (infection or colonisation) are frequently observed in potential deceased donors and the risk of transmission should be remembered. Direct kidney damage in abdominal trauma (e.g. rupture) may result in irreversible kidney failure and limit the use of such grafts. Acute illness and acute episodes of renal hypoperfusion (e.g. with asystolic or hypotensive periods) may result in reversible renal failure due to acute tubular damage. In such cases, diuresis often remains and full renal function returns, even if renal replacement therapy is temporarily required. However, patients with renal cortical necrosis do not regain renal function and remain anuric. Nephrolithiasis does not exclude kidneys *per se*; it requires an individual decision. Therefore final determination should be done during procurement.

c. *Renal function and biochemistry*

Blood and urine sampling and biochemical analysis for general donor assessment should be performed as outlined in Chapter 6 (see §6.2.3) and Table 6.1. Specific blood tests that are especially important in the evaluation of kidneys for transplantation include creatinine, urea, renal clearance (estimated or measured) and electrolytes. If indicated, biochemical parameters of rhabdomyolysis should be evaluated (e.g. creatine kinase (CK), myoglobin). In the urine, special attention should be paid to albumin and albumin/creatinine ratio. Relevant microbiological samples and cultures (e.g. bacteria, fungi, virus) from the donor must be secured, and screening for transmissible infections and multi-resistant bacteria is mandatory. Special consideration should be given to clinical parameters such as haemodynamic status, diuresis, hydration status and recent pre-existing cardio-circulatory events which can cause abnormal laboratory parameters. It is mandatory to take into account data taken in a stable medical condition from before hospital admission because the laboratory values may not be representative of renal function in cases of haemodynamic deterioration or volume depletion (for example, details of pre-admission creatinine and urine albumin/creatinine ratio). In cases of chronically impaired kidney function or older donors, biopsies may be performed to determine the nature or extent of any underlying disease. This may exist if during the previous three months, according to KDIGO Guidelines [39], either severely decreased kidney function or severely increased albuminuria (e.g. > 30 mg albumin/g creatinine or > 1 g protein/g creatinine in the urine), or both moderately decreased kidney function

and moderately increased albuminuria, have been observed in steady state as outpatient. Unfortunately, this cannot be concluded when only the data of the most recent hospital stay at the intensive care unit (ICU) are available. Note that advanced, irreversible, chronic renal failure is a contraindication for donation.

Acute impairment of donor renal function sometimes occurs as a reversible complication of the acute illness or disease and may not necessarily be a contraindication for renal donation. In cases of acute tubular damage without cortical necrosis, transplantation results are good [40-42]. However, such grafts will often show prolonged DGF and require dedicated post-transplantation support. Renal function and diuresis may recover despite the temporary need for renal replacement therapy, and outcome may not be impaired [43-44]. Kidneys should not be used if anuria persists for several days and after intra-operative inspection of the kidney indicating irreversible necrosis with histopathological confirmation (expert opinion).

In cases with direct muscular damage (e.g. trauma, pressure, infection, cramps) or muscular damage secondary to ischaemia (e.g. asphyxia, suicide by hanging, asystole, hypotensive shock), rhabdomyolysis and myoglobinuria may occur. This might lead to acute renal tubular insufficiency and renal failure. In donors with acute kidney injury with no history of other kidney disease, grafts exposed to rhabdomyolysis can still be used for transplantation at a higher risk for DGF [45].

d. *Imaging pre-procurement*

The morphologic description of the kidneys and urinary tract can be performed by abdominal ultrasound (with quantitative measurement of: length × width × parenchyma thickness + structure) or by computer tomography (CT) as outlined in §7.2.1.2a. and §7.2.1.2b.

e. *Donor maintenance*

Avoiding acute kidney injury by proper donor management should be a key goal of management (see Chapter 5).

Due to its anti-oxidative properties, donor pre-treatment with low-dose dopamine over 6-7 hours pre-procurement may be of benefit for outcomes in kidney as well as other organ transplants [46-52].

The role of mild controlled therapeutic hypothermia in organ donors has been explored. Despite reduction of the rate of DGF in kidneys from all DBD donors, hypothermia only improved one-year graft survival in non-ECD donor kidneys [53].

f. *Macroscopic kidney appearance at procurement*

Consideration should be given to the macroscopic appearance of the graft (smooth surface or scars, evaluation of cysts, adhesions to adjacent peri-renal fat due to antecedents of inflammation), colour before and after perfusion, anatomical variants, vascular structure and atherosclerosis of the aorta and renal artery. In cases of suspicious findings (e.g. tumour, space-occupying lesion), additional imaging and biopsy may be recommended.

In every case of a solid mass which is not normal renal parenchyma or cyst, malignancy should be ruled out; the mass should be removed with an appropriate safety margin and with preservation of the remaining parts of the graft. This so-called 'Ro resection' permits histopathological investigation and possible subsequent transplantation of the kidney(s) (see §9.4.25 and §9.2 for further details). Whenever malignancy is suspected, then the final release of the affected kidney for transplantation should be after the preliminary results of histopathological examination by frozen section become available. This does not preclude shipment of the graft to the intended recipient centre in order to limit ischaemia times. It is essential to inform the recipient centres (of all other organs procured from the same donor) that a suspicious lesion has been identified. This issue should not result in discard of organs and it is advisable to perform case-by-case individualised decisions.

A major issue is the degree of arteriosclerosis of the renal artery allowing anastomosis or not. However, this depends on the opinion and skill of the transplanting surgeon and the decision should therefore be left to the surgeon of the accepting centre.

Note that limited warm ischaemia time may be acceptable for kidneys, as we know from experience with controlled DCD kidneys, especially if it stays well below 20 minutes; however, it becomes critical when exceeding 120 minutes (see Chapter 12). Hence, the occasional circulatory arrest that may occur before the start of *in*

situ preservation in a DBD donor is not by itself an absolute exclusion criterion.

g. *Kidney biopsy*

There are three different scenarios in which biopsies are performed:

- Firstly, most often, kidney biopsies are taken at procurement for characterisation of space-occupying lesions and exclusion of malignancy: an R0 resection should be attempted as outlined above in 7.2.1.1.f Macroscopic kidney appearance at procurement.
- Secondly, sometimes, a kidney biopsy can be used to exclude acute cortical necrosis or a suspected specific chronic kidney disease.
- Thirdly, pre-implantation biopsies should not be undertaken systematically, because the added value of routine graft biopsy is limited when it comes to predicting intermediate or long-term renal function [10, 17-18, 54-62]. Systematic reviews and other reports have concluded that the knowledge derived from a biopsy does not substantially contribute to the prediction of graft survival [10, 17, 56-64]. Therefore, it is inappropriate to discard kidney grafts for transplantation exclusively on the basis of procurement biopsy results [61-62, 64-67].

  In cases where a biopsy is performed to assess the graft, it is recommended to adhere to the Banff classification so the results can be compared in a post-transplant evaluation of the recipient if necessary [56, 63, 68]. The minimum dataset includes the number of glomeruli investigated, the degree of glomerulosclerosis, interstitial fibrosis, arterio-/arteriolosclerosis and tubular atrophy/necrosis. On the one hand, no consensus exists about the prognostic relevance of biopsies. On the other hand, the knowledge of age-adjusted normal "appearance" of a kidney biopsy in donors older than 80 years might facilitate the decision to accept such grafts for single or dual renal transplantation, for a properly matched recipient. Currently we lack systematic research and reliable data on this subject.

  Note that some transplantation units use graft biopsies in the assessment of kidneys retrieved from older donors and donors with cardiovascular risk factors (e.g. history of hypertension, ischaemic heart disease, peripheral vascular disease or diabetes). Mild histological changes, with minor glomerular sclerosis, minor interstitial fibrosis, mild arteriosclerosis or minimal tubular atrophy, may be acceptable. Some transplant groups apply, as renal quality criteria, the histological score described by Remuzzi *et al.* that allows the classification of kidneys as unsuitable or suitable for transplantation as single graft or as double graft [24].

h. *Other issues*

En bloc and single kidney transplantation from small paediatric donors (e.g. < 10 kg) has been demonstrated to be possible and successful [11-14, 69-73], even when the two small grafts are used in two different paediatric recipients [12]. Both kidneys can be procured *en bloc* or separately, but the procurement/transplant surgical teams should be familiar with paediatric transplantation as well as micro-surgical technique (for implantation) of the two grafts in one or two recipients. In properly procured *en bloc* kidneys from small paediatric donors it is not optimal to discard one kidney for the purpose of generating a vascular patch for the other graft; both should be used.

In grafts procured from advanced age donors (e.g. > 80 years), there is no consensus on whether they should be used together for one recipient or separately for two recipients [10, 17-18, 24] nor on which criteria to use to guide this decision.

In controlled and uncontrolled DCD, despite exposure to prolonged 'warm' ischaemic episodes, functional recovery of the kidney is possible without impairment of long-term function [74-80] although DGF may occur (see Chapter 12).

Scoring systems for expanded donor criteria have been developed in some countries (e.g. USA). They require adjustment to the donor and recipient populations in a specific country and they should not be abused as deferral criteria. Grafts from ECD donors with high score values may provide acceptable outcomes with a benefit for the recipient when a proper match between donor risk factors and recipient risk factors has been performed [18, 31-35, 59, 81-85]. Scoring systems – with or without adding biopsy results – currently fail to provide appropriate cut-off values indicating when to accept or to discard a kidney [61-62, 64-67, 86-89]. Instead of trying to avoid all risk but with increased discard rates, surgeons should remember that some recipients have a survival benefit when receiving a graft with high score

Figure 7.1. **Suggested reporting workflow for minimum dataset to be communicated when performing abdominal investigation with ultrasound, CT or MRI [92]**

Liver	size MCL (cm)	*only if not measured:* size in relation to MCL (medio-calvicular line): normal/small/large/enlarged/n.a.
	parenchyma	normal/slightly hyperechogenous/severely hyperechogenous (relevant steatosis)/cirrhosis/n.a.
	space-occupying lesion	no/yes/n.a.
		if yes: kind of lesion: tumour/abscess/angioma/contusion/cyst/n.a./unspecified (multiple entries)
		location: segments
		further details
	liver edge	sharp/blunt/n.a.
	intrahepatic bile ducts	normal/dilated/n.a.
	portal vein	open/thrombosis or obstructed/n.a.
	remarks	*only further information not described above should be added*
Gall-bladder	status	normal/cholecystectomy/cholecystitis/cholecystolithiasis/cholecystitis & cholecystolithiasis/n.a.
	space-occupying lesion	no/yes/n.a.
		if yes: kind of lesion: tumour/abscess/angioma/contusion/cyst/n.a./unspecified (multiple entries)
		further details
	extrahepatic bile duct	normal/dilated/choledocholithiasis
Pancreas	parenchyma	normal/lipomatosis/oedema/fibrosis/n.a.
	calcifications	none/yes/n.a.
	signs of pancreatitis	none/yes/n.a.
	space-occupying lesion	no/yes/n.a.
		if yes: kind of lesion: tumour/abscess/angioma/contusion/cyst/n.a./unspecified (multiple entries)
		location: head/corpus/tail/multiple lesions/n.a.
		further details
	remarks	*only further information not described above should be added*
Kidney right	measurements	**length (cm), width (cm), thickness of parenchyma (cm)**
	only if not measured:	normal size & parenchyma/thin, atrophic parenchyma/atrophic kidney/nephrectomy/n.a.
	hydronephrosis	none/yes/n.a.
	nephrolithiasis	none/yes/n.a.
	space-occupying lesion	no/yes/n.a.
		if yes: kind of lesion: tumour/abscess/angioma/contusion/cyst/n.a./unspecified (multiple entries)
		location: upper pole/middle section/lower pole/multiple lesions/n.a.
		further details
	remarks	*only further information not described above should be added*
Kidney left	measurements	**length (cm), width (cm), thickness of parenchyma (cm)**
	only if not measured:	normal size & parenchyma/thin, atrophic parenchyma/atrophic kidney/nephrectomy/n.a.
	hydronephrosis	none/yes/n.a.
	nephrolithiasis	none/yes/n.a.
	space-occupying lesion	no/yes/n.a.
		if yes: kind of lesion: tumour/abscess/angioma/contusion/cyst/n.a./unspecified (multiple entries)
		location: upper pole/middle section/lower pole/multiple lesions/n.a.
		further details
	remarks	*only further information not described above should be added*
Other	Aorta morphology	normal/abnormal/n.a.
		if abnormal: arteriosclerosis/aneurysm/stenosis
		further details
	Vena cava	
	free fluid or ascites	none/moderate/significant/n.a.
		if free fluid: location and amount in abdomen
	remarks	*only further information not described above should be added*

n.a. = not assessable.

values compared to staying on dialysis [65, 90] or associated with some infectious disease-transmission risks [91].

7.2.1.2. *Imaging in the context of abdominal graft evaluation*

a. *Abdominal ultrasound*

Abdominal ultrasound (sometimes contrast-enhanced) can be performed as a safe bedside method in the ICU, but taking into account the well-known limitations of its sensitivity and specificity (see Table 7.1). A proposal

Table 7.1. **Parameters to be considered when performing abdominal ultrasound in the assessment of organ donors**

Abdominal ultrasound sonography	Comment, informative value
Reliability concerns	Quality of investigations can be limited due to obesity, intestinal overlay (intraluminal gas) or inability to position the donor properly for investigation.
Space-occupying lesions/ tumours/ malignancies	In any case of a space-occupying lesion, the findings must be verified by intra-operative inspection and histopathology when indicated. A CT scan might be helpful to search for possible metastases elsewhere (e.g. in case of a suspected primary renal cell carcinoma) or a primary tumour in another location (e.g. in case of suspected metastases).
Aortic vascular anatomy	Aneurysm and arteriosclerotic plaques are indicative of systemic arteriosclerosis. Within this examination there should be checks for vascular abnormalities and/or arteriosclerotic plaques in the arteries supplying the organs.
Kidneys and urinary tract	Standard description plus quantitative measurement of kidney length, width and parenchymal mass (thickness). Anatomic variants should be highlighted (e.g. horseshoe kidney). Signs of outflow obstruction?
Liver and biliary tract	Standard description plus size in mid-clavicular line, liver edge. The comparison of echogenicity of liver to kidney parenchyma (probability of macro-vesicular steatosis elevated in cases of non-homogeneous or enhanced echogenicity of liver parenchyma compared to kidney parenchyma). Also status of portal vein, perfusion in the liver, intrahepatic and extrahepatic bile ducts should be assessed. Statements about exact size and volume are helpful for considering split liver transplantation.
Pancreas	Standard description should include statement about intra-parenchymal fat if possible.
Intestine	Standard description.
Fluid in the abdomen, pleural effusion, evidence for haematoma, lymphoma, abnormalities in lower pelvis (e.g. ovaries, prostate, urinary bladder), status of the spleen	This relevant information is for the general assessment of the donor.
Inferior vena cava	Information about fluid status of the donor (donor maintenance).

for a standardised dataset to be communicated when performing abdominal radiological investigations during organ assessment is outlined in Figure 7.1 and an example questionnaire can be found in Appendix 14.6. The abdominal radiological examination includes the whole abdomen for general donor assessment (tumours, lymph nodes, fluid, bleeding, aneurysms, arteriosclerosis etc.) as well as the individual organs (e.g. liver, kidneys, pancreas). Following an examination with whole-body CT scan, abdominal CT scan or magnetic resonance imaging (MRI), a re-evaluation of the donor and the individual organs should be undertaken. Beyond investigation for space-occupying lesions or malignancies, the results and findings of CT and MRI exams could be communicated using a similar template as that suggested for abdominal ultrasound (Figure 7.1). According to the recommendations of Chapter 9, a recent whole-body CT scan helps to rule out unexpected metastasis in donors with a previous history of malignancy.

b. *Abdominal CT scan*
This is normally not required in the assessment of a donor unless a whole-body or abdominal CT scan is specifically indicated by the guidance in Chapter 9, or for the characterisation of an unexplained space-occupying lesion (exclusion of malignancy) as well as infection. If such investigations are performed, a re-evaluation of the donor and organs should be performed. With this more detailed information, the issues outlined as suggested for abdominal ultrasound (see 7.2.1.2.a and Table 7.1) can be examined. Note that a pre-procurement CT scan helps to identify suspect space-occupying lesions at an earlier stage, which may help to exclude malignancies [93] but carries the risk of detection of new non-specific lesions. Also additional information about anatomical variants can be provided. Performing routine CT scans in donors remains controversial in some European countries (see §6.7).

7.2.2. Liver selection criteria

a. *Donor age*
There is no age limit (in very young and elderly donors) although with increasing donor age the risk of failure may be elevated due to arteriosclerosis of the small vessels of the biliary tract and increased frequency of ischaemia-type

biliary lesions (ITBL) [94-121]. In the context of accepting older donors, an accumulation of other donor- or recipient-related risk factors should be avoided [122-125].

Age-related atherosclerotic changes have a low impact on the function of the hepatocyte due to its double perfusion (arterial and portal-venous) in the absence of metabolic disease, e.g. diabetes or hyperlipidaemia. Literature supports the use of liver grafts from the upper extremes of age [126-128] when biopsy excludes relevant fibrosis, macro-vesicular steatosis etc. With advanced age, the prevalence of obesity increases [129] as well as the risk of macro-vesicular steatosis of the hepatocyte – which is observed in 9 % to 26 % of procured livers [130], with many more not procured because of steatosis. When biopsy reveals a macro- vesicular steatosis > 30-60 %, excessive cytoplasmic fatty acids may lead to increased lipoperoxidation on reperfusion yielding more free radicals, which in turn leads to damage of the cellular architecture, Kupffer cell activation and concomitant pro-inflammatory upregulation [131-132]. This causes poor outcomes when grafts are used with such moderate or severe steatosis in addition to the ischaemia-reperfusion injury after implantation of the graft [133].

Techniques aimed at improving organ preservation and enabling *ex situ* organ evaluation can be considered in cases with older donors and steatotic livers (e.g., machine perfusion of livers) [134].

b. *Past and current medical history*

Prior viral, alcoholic or fatty liver disease, previous hepato-biliary surgery, uncontrolled abdominal infections, long-term hepatotoxic or acute liver failure causing medication, intoxication affecting liver function, acute or chronic right heart failure and liver trauma are considered as risk factors for inferior outcomes after liver transplantation. Lifestyle conditions, ethnicity, country of origin and travel history should be considered; beyond increased risks of infectious disease transmission, these may be a hint of potential graft damage.

Systemic or other disease related to other organs may compromise the liver in quality and function or may be an indicator of undetected liver disease (e.g. diabetes, metabolic syndrome, obesity → non-alcoholic fatty liver disease (NFLD) or steatohepatitis; ulcerative colitis → primary sclerosing cholangitis).

The following conditions do not preclude liver donation, but require consideration as to whether acute necrosis of the hepatocyte occurred or not: recovery from previous acute cardiac arrest or hypotensive periods, use of vasopressors, acute kidney injury etc. [1]. An ICU Stay > 7 days used to be an assumed risk factor [1] but with appropriate ICU therapy this becomes a neglectable issue.

ECD donors are assumed to be associated with an increased risk of DGF or PNF [135-136] since compromised liver grafts have a poor tolerance of ischaemia reperfusion injury (IRI) [137] due to complex pathophysiological interactions [138]. From clinical experience, the ECD criteria associated with increased graft failure rates are donor age > 65 years, serum sodium > 155 mmol/L [139], macro-vesicular steatosis > 40 %, cold ischaemic time > 12 h [104, 112-113, 133, 140-142], split-liver grafts [143-144], DCD grafts or haemodynamically compromised donors. Nonetheless, experienced transplant centres overcome such restrictions and successfully use grafts from donors with a hospital stay > 7 days, body mass index (BMI) > 34.9 kg/m^2, maximum ALT or AST (alanine or aspartate aminotransferase) > 500 IU/L and maximum bilirubin > 2.0 mg/dL [126].

The issue of using livers from donors recovering after significant poisoning or intoxication is discussed controversially, but after careful donor selection no negative impact on graft survival may be observed [145].

c. *Liver function parameters*

Consideration should be given to liver transaminases (ALT or AST: both non-specific liver function tests), gamma-glutamyltransferase (γGT: cholestasis, may be elevated in NFLD or fibrosis) [146-149], serum bilirubin (cholestasis), alkaline phosphatase, lactate dehydrogenase (LDH: any necrosis), albumin and coagulation tests (e.g. INR: liver function). Evaluation of liver enzymes should take current and past clinical history into account with respect to hepatic and non-hepatic causes of deviation. Please refer to Table 6.1 in section 6.2.3 for more details.

Hypernatraemia as a complication of diabetes insipidus has been reported to be associated with a high probability of PNF [124]. The critical effect on the graft is thought to be the result of cell swelling, increased osmolality during IRI. As a result, high sodium levels during

the donor's stay in the ICU are a significant factor for PNF, and not only the last sodium value before procurement [139]. Whether only the single factor of avoiding hypernatraemia or the effect of including this issue as part of aggressive donor management (see Chapter 5) has contributed to reducing the rate of PNF has not been confirmed well in studies. From a theoretical point of view the area under the curve caused by sustained periods of hypernatraemia should be of a different impact compared to single peak values for a short time. Interestingly, large database researches in UNOS [143] and Eurotransplant [146] could not find any association between hypernatraemia and graft failure.

Abnormal liver biochemistry *per se* does not exclude the use of these organs for transplantation [8, 146, 148-149]. Very high levels of transaminases indicate a recent ischaemic insult, probably due to hypoperfusion or hypoxia, that is seen in patients with cardiorespiratory arrest. Adequate circulation and oxygenation by resuscitation helps compensate for this event, allowing recovery from dysfunction, especially in younger donors [150]. Metabolic acidosis in the presence of abnormal liver biochemistry is generally an unfavourable combination. There are no definite guidelines on the upper limit of acceptable abnormal biochemistry, but a downward trend in liver enzymes is assumed to be indicative for recovery of the liver from such events. This can be measured by blood tests at least 12 h apart. With novel preservation techniques available, grafts with severe dysfunction prior to procurement can be assessed and resuscitated *ex situ* (see Chapter 11).

d. *Imaging and liver morphology*

Liver ultrasound (see §7.2.1.2a. and Figure 7.1) may be used to exclude obvious fatty livers, cirrhosis and fibrosis or any morphological abnormality, while the low rate of sensitivity and specificity is well known. An abnormal ultrasound result should be confirmed by intra- operative inspection (together with histopathologic confirmation if indicated). It is very helpful to provide data about the perfusion status of the organ, status of portal vein, intra- and extrahepatic bile ducts, and liver size (in particular of the left lateral lobe when a split procedure is intended). If available, the abdominal CT scan should be re-evaluated with this question in mind.

CT scan or ultrasound is of value to measure the size of the liver (anterior–posterior measurement, which facilitates the size matching of larger donors to smaller recipients).

If a split procedure is intended, a CT scan of the donor provides valuable information about the vessel and bile duct anatomy; use of magnetic resonance cholangiopancreatography (MRCP) is also helpful).

e. *Macroscopic appearance and perfusion at procurement*

It is important to evaluate the sharpness of the liver edge, and the colour and consistency of the liver before and after correct perfusion. Obvious liver fibrosis and cirrhosis or steatosis may exclude transplantation. It is very difficult to estimate the degree of steatosis with only visual inspection. The degree of macrovesicular fatty degeneration as well as fibrosis (according to Ishak score) can be evaluated and confirmed by using peri-operative biopsies (frozen section) [94-96, 103, 110, 151-155]. A rose-like colour with change to yellow after cold flush during organ preservation is associated with a higher probability of macro-vesicular liver steatosis [112].

Some limitations exist due to inter-observer variation or due to unrepresentative samples caused by a more or less focal pattern of a lesion (e.g. sub-capsular biopsy) [156-157]. The degree of acceptable fatty degeneration for transplantation may depend on the general conditions of the donor and recipient, and anticipated cold ischaemic time, and may vary with the experience of the transplant team [158-159]. Unfortunately, there is no consensus on criteria for determining the extent of fatty change of the liver. Most transplant surgeons rely more on their subjective impression, through the graft procurement process, than on histology. This might hold true for detection of the degree of macro-vesicular steatosis, but it requires some experience and training. Nevertheless, histopathologically confirmed moderate macrovesicular steatosis exceeding 30 % to 60 % of the parenchyma surface is considered as a significant risk factor for DGF and PNF [131, 155, 160-162]. Other forms of steatosis (so-called micro-steatosis with small fat droplets not displacing the cell nucleus) are considered as a minor issue [131, 140, 152, 155-156, 163-165] unless

the disease is associated with an underlying liver disease causing liver failure with fat accumulation in the cell in a kind of 'fat-foam' [140, 157, 163]. The issue of micro-vesicular steatosis is outlined below.

Allocation of a liver with some (macro-vesicular) fatty change might not be advisable for a recipient not likely to survive in cases of DGF, PNF or re-transplantation, whereas allocation to another recipient in a more advantageous clinical status may be acceptable, depending on the risks of waiting for the next available organ and avoidance of other risks, such as donor diabetes or long ischaemia time > 5-6 h [140, 166-167]. There is no consensus on the use of such critical grafts and selection of the appropriate recipient. The major issues in using grafts with moderate macro-vesicular steatosis are the complications of the post-reperfusion syndrome in the recipient, together with DGF and PNF [167-169].

In elderly donors the liver parenchyma may have a 'funny colour' [112] and it might rupture due to its fragile consistency when extensive traction is applied at surgical manoeuvres.

Severe arteriosclerosis may not harm the hepatocytes but it is a risk factor for damage to arterioles of the small bile ducts. Therefore appropriate flush with preservation solution during procurement must be carried out in any case. How far donor arteriosclerosis is a risk factor for causing post-operative complications, e.g. ITBL, needs further research.

In addition, methods for optimised organ preservation and for *ex situ* organ evaluation may change considerations discussed in this section about conclusions on when a graft can be used or not for transplantation after organ procurement (e.g., machine perfusion of livers) [134].

Special consideration should be given to frequently found aberrant liver arteries originating from the coeliac trunk and/or superior mesenteric artery and/or aorta. Such vessels must be identified and preserved – so implantation is possible. Documentation on the organ report is important. In this context the impact of harm to other organs and their blood supply must be reviewed. In the worst case agreement must be found between the recipient centres for the relevant organs, e.g. whether the accessory/replaced right hepatic artery from the superior mesenteric artery (SMA) can be divided to favour the inferior pancreatico-duodenal artery supply to the pancreas. This may affect the liver, pancreas, intestine and kidneys.

f. *Liver biopsy*

Liver biopsy is often performed during procurement and processed as a frozen section, although the increasing availability of *ex situ* perfusion machines may enable more informative paraffin sections for analysis. The result must describe the percentage of parenchymal area with cells affected by macro-vesicular steatosis and the extent of fibrosis (by Ishak score). In addition it is helpful to report steatosis with specific regard to small fat droplets, micro-vesicular steatosis, signs of inflammation, necrosis and cholestasis [140, 156].

Beyond inter-observer variation, other reasons why the representative value of a biopsy may not be high are sampling errors (e.g. nodular cirrhosis) or non-representative findings from biopsies taken from sub-capsular liver edge. Furthermore, it is beneficial to discuss with the pathologist how to transport the specimen, because incorrect transport media will cause further inappropriate results. As mentioned in Chapter 6, some countries limit access to pathology services for investigation of frozen section until a time as close as possible to procurement. Therefore there needs to be a balance of risks (e.g. extended ischaemia times due to turnaround times) *versus* benefits from additional information.

Liver biopsy before organ procurement can be done after the declaration of death and after obtaining donation consent, as long as there are no severe coagulation deficiencies and the physician performing the biopsy is very experienced in doing this [170-171].

In the pathology report, the wording used to describe steatosis should clearly distinguish between macro-vesicular steatosis – to be described either as large fat droplets or small fat droplets caused by risk factors responsible for non-alcoholic steato-hepatitis (NASH) – and micro-vesicular steatosis, described as multiple tiny fat vesicles caused by other issues [140, 156, 164-165]. Macro-vesicular steatosis refers to the percentage of liver parenchyma where in the hepatocyte one or a few large fat droplets displace the nucleus to the edge of the cell. Despite lack of consensus, grafts with a degree of such steatosis below 30 % are used for transplantation, whereas in graft where the degree of steatosis is above 30 to 60 % the risk

of PNF increases and grafts with more than 60 % are deferred. In contrast, when one or a few small lipid droplets do not displace the nucleus then the finding should be described as small droplet steatosis, but often the term micro-vesicular steatosis is used. This finding can be ignored as a risk, because it seems not to affect the outcome adversely. Distinguished from this entity should be pure micro-vesicular steatosis either caused by severe diseases with acute liver failure or as a harmless finding in DBD due to agonal and/or ischaemic changes. The morphologic finding is a foamy or vesicular-appearing cytoplasm of very small lipid droplets that surround the nucleus [164-165].

g. *Other issues*
Every healthy liver graft should be considered for splitting into two grafts for two recipients, depending on the anatomy. Splitting criteria for liver have included: age < 60 years, intensive care unit stays < 5 days, low inotropic support and near-normal liver function tests [172]. These have been widened by some centres where the only limitation for a split liver procedure in a liver without morphological changes is the size and vascular anatomy, which requires careful inspection and description by an experienced surgeon.
Scoring systems for ECDs have been developed in some countries based on local data (e.g. the Donor Risk Index in the USA) [143]. They should be validated and require adjustment to the population of the donor country or region [146-147, 173]. Many studies confirm that ECDs do not limit the outcome of liver transplantation after proper recipient selection, despite the known risk of increased graft failure rates [1, 6, 101-102, 105, 110-112, 115, 119-121, 141, 146-147, 173-175]. This requires proper matching of donor and recipient after critical risk–benefit assessment. In such grafts it is pivotal to keep ischaemia times as short as possible because this factor may even further increase the risk of ITBL [104, 112-113, 140-141].
The issue of hepatitis C co-infection of the recipient (e.g. in D–/R+) and the use of otherwise compromised liver grafts will have to be revised [120, 143] when more outcome data become available based on the impact of the new drugs used in hepatitis C therapy which eliminate HCV replication in most cases. Then HCV re-infection of the graft (e.g. in D–/R+) by recipient's circulating HCV-virus may not persist anymore with complications associated to this.
In controlled and uncontrolled DCD the liver can be recovered and transplanted. Compared to DBD there is a higher risk reported for SGF, IGF, PNF and ITBL [1, 176-181]. The duration of warm ischaemia is predictive for outcome, which decreases with every extra minute of asystolic warm ischaemia [177, 181]. Careful decision is mandatory with asystolic warm ischaemia times exceeding 25 minutes [181], although the ability to evaluate livers using novel *in situ* and *ex situ* preservation technologies will remove an arbitrary asystolic time limit (see Chapter 11 and Chapter 12).

h. *Modification by donor management*
Standard intensive care therapy, taking into account the key points already mentioned above and in Chapter 5, will be sufficient to maintain the good quality of the liver graft.

i. *Recipient factors*
Well known are risk factors such as re-transplantation, acute liver failure, deteriorated health status due to chronic liver failure or burden of recipient's co-morbidities. This may influence the selection criteria on an individualised donor–recipient match. Thereby the key question is: Can the recipient wait for another organ offer or is this the last chance, while accepting some risks? This issue cannot be generalised within the scope of this Guide.

j. *Interaction*
In summary, in a compromised liver graft, as outlined above, ischaemia times should be kept as short as possible. Combining the risk factors as outlined above may not contribute to improve outcome. An individualised approach is needed for optimal use of a particular graft in particular recipient.

7.2.3. Pancreas selection criteria

a. *Age and body mass index*
Traditionally many centres are reluctant to use pancreases from donors older than 50 years despite some evidence of good results after careful donor selection [182-184] taking into account past and current medical history (see below). In some countries, donors below the age of 55 years and with BMI < 30 kg/m² are primarily considered for pancreatic whole

organ transplantation, rather than islet preparation [182].

Increasing donor age is associated with a higher failure rate after pancreas transplantation [185-186], which should be seen in the context of remaining on the waiting list. A study reported that the 5-year unadjusted patient survival rate was higher for simultaneous pancreas–kidney transplant recipients from young donors (84.5 % *v.* 81.0 %) [187]. However, the 5-year patient survival rate for those who remained on the waiting list was 45.4 %. In this study, receiving a simultaneous pancreas–kidney transplant from an old donor was associated with a 72 % reduction in mortality compared with remaining on the waiting list. Similar results can be reported from other single centre or registry studies [184, 188-192].

Although higher BMI is considered a risk factor in whole pancreas transplantation, these more obese pancreas grafts have higher yields for islets after isolation and are preferably being used for pancreatic islet transplantation [193].

Adiposity is associated with the risk of intra-pancreatic fat accumulation. This intrapancreatic fat accumulation may contribute to a higher rate of reperfusion damage and post-transplantation pancreatitis, although some centres report acceptable outcomes after utilisation of overweight donors [194].

Beyond the above-mentioned limits of age and BMI, pancreas transplantations have been carried out with success when appropriate retrieval technique, preservation and prophylaxis of ischaemia-reperfusion damage has been applied [194]. Donor age is the highest single risk factor for failure in pancreas transplantation [195-196].

b. *Past and current medical history*

Prior pancreatic disease (e.g. acute or chronic pancreatitis), alcoholism (risk of pancreatitis), biliary tract outflow problems, diabetes mellitus (as absolute exclusion criterion), history of arterial hypertension, adiposity (increased risk for intrapancreatic lipomatosis), active abdominal infection, abdominal trauma (especially deceleration trauma of the mesenteric root), number of days spent in the ICU (increasing probability of development of oedema of the pancreas), cardio-respiratory arrest and resuscitation procedures are discussed as risk factors for inferior outcomes after pancreas transplantation. Appropriate research is still lacking.

Glucose metabolism is frequently dysregulated during ICU care. Therefore insulin requirements during ICU stay within donor-maintenance protocols are without prognostic value in the assessment of pancreases for transplantation. On the other hand, manifestation or new onset of type 2 diabetes mellitus is possible in ICU patients at an age of over 50-65 years.

c. *Pancreatic function*

This may be assessed by factors other than glucose and insulin requirements, pancreatic enzymes and calcium levels during stay in an ICU. Some donor-maintenance protocols recommend insulin treatment, among other hormones. Many patients with severe head trauma become hyperglycaemic and require insulin therapy, despite normal pancreatic function and no history of diabetes.

For laboratory data contributing to characterise the pancreas, please refer also to Table 6.1 (in §6.2.3). In laboratory examination, amylase may be elevated for non-pancreatic reasons and the analysis of pancreas-specific amylase and/or lipase is recommendable. If available, HbA1c measurements reflect the glucose homeostasis of the past weeks more accurately.

d. *Imaging pre-procurement*

This can be assessed by abdominal ultrasonography, magnetic resonance imaging (MRI) or other imaging, e.g. trauma CT on admission (see §7.2.1.1 and Figure 7.1).

e. *Haemodynamic*

Uncontrolled severe hypotension or cardiopulmonary arrest often profoundly compromise the functional quality of pancreases intended for transplantation, but specific conditions apply in the DCD situation (see Chapter 12).

f. *Macroscopic appearance at procurement*

Consideration should be given to the macroscopic appearance, vascular and anatomical changes, and correct perfusion of the pancreas. The macroscopic appearance should be without severe oedema, bleeding, fibrosis or pancreatitis (despite toxic causes and without evidence in imaging or laboratory parameter). Further risk factors for post-transplantation pancreatitis associated with graft failure are peri-pancreatic haematomas, capsular tears and elevated intra-capsular fat content or

induration. Abnormalities of vascular inflow and outflow often exist. In some cases, there might be a conflict of interest in relation to the liver team regarding the procurement of certain critical vascular structures for subsequent pancreas and liver transplantation; in these cases co-operation and good communication are essential. This conflict of interest may compromise pancreas procurement in cases of simultaneous intestinal and liver procurement for other recipients (especially if an aberrant right hepatic artery, that branches off the arteria mesenterica superior, travels through the pancreatic head). Unexpected pancreatitis may be detected.

A pivotal role is played by the procurement surgeon, who should preferably have expertise in pancreas surgery and transplantation (see Chapter 11) [197-198]. The specific details of pancreas procurement technique are summarised in reference [197].

The pancreas is a delicate organ that is easily harmed by careless handling and manipulation during procurement (and transplantation). Minor injuries may be repaired, but in some regions up to 13 % of procured pancreases are discarded after back-table inspection at the receiving hospital [199-200]. Adequate training and certification of donor surgeons is mandatory [201], as successful pancreas transplantation is highly dependent on the quality of procurement of the graft [197-198].

g. *Other issues*

Although risk scores, such as the pre-procurement pancreas allocation suitability score (P-PASS) and the pancreas donor risk index (PDRI), might predict the chance of acceptance of the graft for transplantation, a surgeon with experience from pancreas transplantation should inspect the graft for a definite decision. Note that the P-PASS does not correlate with outcome after transplantation, but the PDRI does [195].

Most risk factors considered critical for liver grafts coincide with risk factors for pancreas grafts (see §7.2.3).

Strict adherence to 'ideal donor criteria' – such as donor age < 40 years, BMI < 30 kg/m^2 or traumatic cause of death – is not compatible with the average donor characteristics nowadays. This will unnecessarily limit the number of grafts available for pancreas transplantation [198]. There is a wide variation in the acceptation and transplantation of pancreases among European countries and regions [202]. Centres with more expertise, reflected by larger transplantation volumes, tend to be willing to accept higher-risk organs [202].

Concepts under discussion that aim to overcome the difficulties associated with non-ideal pancreas donors [186] include video and photographic assessment to allow a decision to be made at the time of retrieval, as well as allocation systems that decrease predicted ischaemia times and enable local experienced pancreas transplant surgeons to inspect the grafts without huge logistic efforts. Then metric donor assessment scores, such as the concept of the PDRI [185], may be helpful to guide decision pathways without increasing the discard rate of potential grafts [194, 192].

Successful results with pancreases transplanted from selected cDCD donors have been reported [203]; see Chapter 12.

Pancreas grafts retrieved from paediatric donors have been successfully used in transplantation to both paediatric and adult recipients, both alone or in combination with liver or kidney [204-205].

7.2.4. Intestinal and multi-visceral selection criteria

7.2.4.1. *Issues in intestinal and multi-visceral selection*

Up to now no standardised definition of ideal donor criteria exists. Often intestinal grafts are transplanted in combination with other organs (e.g. liver, pancreas, stomach, duodenum) and the graft usually includes the ileocaecal valve and/or more segments of the colon (e.g. ascendens, transversum, descendens) [206]. Sometimes the graft may include segments of the abdominal wall (which is discussed further in Chapter 15). Based on a recent review and critical analysis of a national European donor population, the following inclusion criteria can be proposed [8]:

a. *Enteral nutrition*

Enteral nutrition should be initiated in the ICU patient as early as possible when there is no contraindication. In cases of intestinal donation, at least some sterile fluid should be applied to the intestine when passage is tolerated due to missing vagal stimulation of the intestine in DBD [8]. This may be of benefit for the pancreas and other organs too (see Chapter 5).

b. *Age*
Acceptability depends upon local protocols. Some centres have successfully used grafts from donors older than 50 years [8, 207-209]. In any donor aged 0-50 years, intestinal donation must be considered [1, 8, 207]. In the group of donor age > 50-65 years the probability of manifestations of other chronic diseases is increased.

c. *Body weight and donor size*
Donor weight should preferably be lower than recipient weight because most recipients have retracted abdominal cavities. The major obstacle in intestinal transplantation is the size match, in terms of both weight and length, between donor bowel and recipient abdominal cavity [8]. In donors with a BMI > 28 kg/m^2 the probability of elevated intra-abdominal fat is increased.

d. *Past and current medical history*
The criteria are similar to those for liver and/or pancreas donation. Donors should not be obese, nor should they have a history of alcoholism or uncontrolled abdominal infections, prior exposure to toxins affecting small bowel function, severe blunt abdominal trauma (especially deceleration trauma to the mesenteric root), previous intestinal illness or unexplained diarrhoea. There is no evidence for other specific pre-treatment requirements during donor management except for the consideration of enteral nutrition (see Chapter 5) [8]. Recovery from cardiac resuscitation events does not limit donation of the intestine [8, 209]. Prolonged hospital stay (> 7 days) increases the probability of intestinal oedema. At the time of writing, intestines of donors who test positive for SARS-CoV-2 may be offered for transplantation after consultation with the transplantation infectious disease experts (see §8.6.2.19).

e. *Gastro-intestinal and liver evaluation*
Serum electrolytes, liver function tests and liver enzymes should be close to normal values. Evaluation should be undertaken to assure that intestinal motility exists. The continuous use of vaso-active drugs with a vaso-constricting effect should be avoided and weaned off by aggressive donor management. Ongoing abdominal bleeding is a risk factor.
Prolonged hypotension and cardiac arrest may severely compromise the quality of intestinal grafts, but after recovery from such conditions intestinal transplants have been performed successfully [8, 208-209].

f. *Imaging and intestinal morphology*
This can be assessed by abdominal ultrasonography to exclude ascites, other lesions and tumours (see §7.2.1 and Figure 7.1). CT scan may be used when appropriate, especially to evaluate complications due to blunt abdominal trauma.

g. *Macroscopic appearance at procurement and perfusion*
Macroscopic appearance, intestinal peristalsis, exclusion of oedema, vascular and anatomical changes and correct perfusion should be examined. It must be remembered that most recipients of intestinal grafts require an individually tailored graft and that anatomical structures usually dissected from other standard organ recoveries must be preserved, e.g. ascending and transverse colon and all mesenteric vessels. It is advisable to have the surgeon responsible for intestinal procurement and transplantation present throughout the operation. Assessment by an experienced intestinal transplant surgeon is mandatory from start until end of procurement (e.g. procurement procedure is different if colon is included in the graft).

h. *Other issues*
Very often intestinal grafts will be transplanted as a package that includes more than the small intestine with/without colon (e.g. liver, pancreas, stomach, duodenum). Therefore all these organs must be included in the allocation process regardless of donor age and other circumstances (except for legal issues like consent to donation restricted to specific organs).
Currently there are no reports of DCD intestinal donations.
There is widespread confusion over what is an ideal intestinal donor [8]. Current ideal donor criteria are [8, 208-209]: age < 50-60 years, CPR below 10 min, ICU stay < 2 weeks, low doses of vasopressors, normal liver function tests and sodium level < 155-165 mmol/L. Very often, intestines from donors not fitting into this set of ideal donor criteria have been used successfully. Unfortunately, recipients' determinants such as size-match, ABO-match and HLA sensitisation limit the chances for transplantation. Intestinal procurement requires a highly interacting

multidisciplinary team [8]. For donor management, it is important to consider enteral nutrition if possible (see Chapter 5). The limitation is that intestinal paralysis occurs in many donors due to the lack of vagal stimulation.

7.2.5. Heart selection criteria

7.2.5.1. *Issues in heart selection*

a. *Age*

The probability of coronary artery disease (CAD) and other cardiac pathologies increases with age beyond the seventh decade of life. This limits the number of advanced-age heart donors [210-220], although some successful transplants have been reported [210, 213-215]. Some guidelines [221] and reviews [222-223] conclude that using grafts from increased donor age requires an individual risk–benefit assessment comparing waitlist mortality with post-transplant survival in the individual case because availability of heart grafts is limited.

b. *Past and current medical history*

Myocardial infarct, severe valve abnormality [218, 224] (see below), CAD with diffuse sclerosis, severe stenosis of multiple vessels or stenosis at critical location, dilated cardiomyopathy, endocarditis without option for intervention etc., and chronic right and left ventricular dysfunction all exclude heart donation. Minor morphologic abnormalities (e.g. patent foramen ovale, atypical venous drainage of coronary vessel, previous correcting heart surgery) require a case-by-case decision. Minor heart-valve disorders can be corrected before transplantation in some cases.

The risk of coronary sclerosis starts to increase at an age beyond 44-55 years in cases where there are other risk factors (high blood pressure, diabetes, tobacco use, even more in combination with alcohol abuse, age, hyperlipidaemia, cocaine abuse) to be verified by donor evaluation; minor stenosis and wall sclerosis detected by coronary angiography require a case-by-case decision. Minor luminal wall irregularities in coronary arteries or single-vessel stenosis of lower degree do not preclude heart donation for a recipient properly selected and assessed by an experienced heart centre when wall motion disorders and other risk factors can be ruled out.

Severe left ventricular hypertrophy (LVH) is a risk factor (IVSd >16 mm in adults), moderate hypertrophy a minor risk (IVSd 12-16 mm in adults). There is a correlation between quality in treatment of arterial hypertension and LVH.

Valve pathologies exceeding Grade 1 insufficiency are only an exclusion criterion after confirmation by an experienced heart transplant centre. Grade 1 insufficiency is a frequent finding in brain-dead donors.

Arrhythmia or diseases with arrhythmogenic potential (e.g. confirmed long QT-syndrome) limit the success of transplantation [221]. Arrhythmogenic hearts without other morphologic alterations may not be used for every recipient since the risk of 'arrhythmia transmission' still exists despite consideration of implantation of automated implantable cardioverter–defibrillator.

In persistent or permanent atrial fibrillation or conduction disorders, hearts should be carefully examined to exclude underlying heart diseases (e.g. CAD) [221].

Regarding acute events, proper recovery – from trauma, cardiac resuscitation, temporary arrhythmias or broken heart syndrome due to neuro-cardiac lesions (reduced left ventricular function, wall motion disorders, stunned myocardium) or temporarily impaired right or left ventricular function – does not preclude heart donation. The recovery period might take a few days (consider serial monitoring by echocardiography) [221-222, 225-228]. In the right ventricle, acute dilation caused by acute events of pulmonary hypertension might cause irreversible damage.

In this context the use of inotropic catecholamines to treat decreased cardiac output might not lead to a successful transplantation [229] (e.g. > 10 µg/kg/min dopamine or dobutamine as well as > 0.2 µg/kg/min norepinephrine for longer time intervals pre-procurement) while the use of catecholamines to treat peripheral vasodilation may not limit successful transplantation [221-222, 227, 230-231]. In contrast, newer studies [224, 232] conclude that the above-mentioned limits are too low, too conservative and outdated.

Heart contusion, due to direct thoracic trauma or after cardiac resuscitation manoeuvres detected during procurement or by imaging, may preclude heart donation.

Critical assessment of recovery and successful detoxification is mandatory in donors with

acute poisoning from carbon monoxide or other agents before a heart is excluded (see Chapter 10).

The complications of temporary neurocardiac injury after devastating cerebral injuries, with or without cardiac arrest, must be taken into account as one reason for a reversible increase in heart enzymes [220-221]. Because the level of creatine phosphokinase in muscle/brain (CPK-MB) has no significant impact on patient survival, the suggestion of characterising donor hearts by determining CPK-MB may be outdated. CPK-MB values may be increased due to brain tissue necrosis or the fact that measurement differs between laboratories. Other more heart-tissue-specific parameters exist, e.g. Troponin [231], but increased donor Troponin levels themselves should not preclude heart transplantation because experienced centres achieve acceptable results after appropriate recipient selection and short ischaemia times [220]. B-type natriuretic peptides (BNP or NTproBNP) concentrations may correlate with temporarily compromised heart due to acute reversible neuro-cardiac injury also seen in serial echocardiography etc., but prognostic conclusions about later outcome in a recipient transplanted are controversial [221-222]. The failure of cardiac biomarkers to provide information about graft quality is due to the lack of appropriate studies [221-222].

The particular complication of brain-stem coning is a terminal event occurring in devastating cerebral lesions that results in death confirmed by neurologic criteria (see chapters 2, 3, 5).

Further consequences of the autonomic storm during or after brain-stem coning are an imbalance between myocardial oxygen demand and supply, which triggers metabolic functional alterations and sometimes anatomical heart damage (myocytolysis and micronecrosis) [233]. Temporary electrocardiographic signs of myocardial ischaemia, conduction abnormalities and arrhythmias are also common during this period of intense catecholamine release and may require no treatment [227, 234-235]. Insufficient secretion of antidiuretic hormone after brain death is associated with haemodynamic instability and compromised organ function. Low-dose arginine vasopressin results in reduced inotropic requirements and has been associated with good graft function [236]. Methylprednisolone i.v. remains beneficial [235].

Many hearts are declined due to temporarily poor left ventricular function but, after optimal management, left ventricular function can completely recover over time in the donor and allow heart transplantation [211, 221-222, 228]. Although echocardiography is very effective as a snapshot assessment of function, assessment can also be achieved by invasive haemodynamic investigations (see Table 5.1, Table 5.2) which may help in weaning off inotropes. Note that ISHLT guidelines [232, 237] and other studies/reviews [219-223] conclude that donor inotrope use does not impact graft survival but also that hearts with an ejection fraction (EF) > 40 % or minor wallmotion abnormalities can be used successfully for transplantation.

Paradoxically, hypotensive periods in donors have not been associated with inferior graft and patient survival, and neither have many other factors – such as cardiac resuscitation, application of norepinephrine or other catecholamines, donor medication or anti-*Cytomegalovirus* status – when the donor had been assessed and managed properly [219].

Careful donor and recipient selection should be carried out, especially in donors with recovery from cardiocirculatory instability while adhering to recommendations [238]. It should be decided at transplant centres whether an offered heart graft for a particular recipient will be of benefit or not, taking into account the actual health status of the recipient.

A proper weight/size match between donor and recipient improves the outcome of heart transplantation [237], but there is a broad range within the limits accepted [232].

c. *Investigation for acute myocardial ischaemia*

This should include tests for biomarkers changes as outlined in the previous section, which should take clinical history and evolution into account. Minor elevations are frequently observed in DBD and this should be distinguished from significant elevations typical for myocardial infarct. In major elevation, complications of CAD should be considered [221].

Electrocardiograms should be normal or should become normal. Atypical re- polarisation can be accepted, especially when clearly related to cerebral complications [224]. In DBD, due to failure of the vagal tone, sinus tachycardia of about 100 per minute is a normal finding and

should not prevent further investigation of the donor.

Due to the interaction with temporary neuro-cardiac injury in DBD, interpretation of changes typical for myocardial ischaemia must be done carefully in order to avoid misinterpretation of reversible temporary neuro-cardiac injury with morphological changes causing myocardial ischaemia.

d. *Imaging and morphological examinations pre-procurement*

Echocardiography should evaluate morphology, contractility and function of both ventricles and atriae, left ventricular ejection fraction (measurement of the ejection fraction or shortening fraction), wall-motion disorders and valve anatomy. Hypertrophy should be measured quantitatively (e.g. diastolic thickness of intra-ventricular septum). The haemodynamic status of the donor should be stabilised before decisive echocardiography is performed [225, 239]. Note that, at bedside in ICU in donors with tachycardia, some quantitative measurements of the left ventricle are possible (see above) whereas in the right ventricle qualitative assessment is possible and sufficient, but attempting to take quantitative measurements is challenging and resource-consuming.

In echocardiography, serial monitoring is recommended in case of temporary LV-dysfunction and regional wall abnormalities in order to monitor recovery from temporary neuro-cardiac injury. An EF > 40% does not exclude heart donation as well as minor wall-motion abnormalities [232, 237], especially when of a temporary nature [221-223, 240].

Coronary angiograms are advisable in donors aged above 55 years and/or if there is a significant risk factor for CAD, e.g. male donors over the age of 55 and females aged over 55 with one or more risk factors for CAD, as well as donors of either sex aged between 45 and 55 years if more than one risk factor for CAD exists [218, 225-226, 236, 239, 241-242]. However, the absence of coronary angiogram data is not necessarily a cause for excluding a potential heart donor. The indication for coronary angiography must be balanced against the risks associated with complications introduced by investigation and transfer of donor to laboratory – e.g. requiring in the lungs afterwards special recruitment manoeuvres (see Chapter 5, §7.2.6.1e).

Adenosine stress echocardiography may contribute to assessment of stress-induced wall-motion abnormalities as an alternative diagnostic tool to coronary angiography [221-222, 226, 243].

e. *Haemodynamic monitoring during resuscitation and donor maintenance*

This should include evaluation of blood pressure, oxygen saturation, haemoglobin, hypotension, occurrence of cardiac arrest, use and dosage of inotropic and vaso-active drugs, central venous pressure and invasive haemodynamic measurements, where appropriate. This is done anyway in the context of proper donor management (see Chapter 5). Invasive haemodynamic monitoring may be performed for donor management as well as functional assessment in series too.

Donor pre-treatment with low-dose dopamine may be of benefit for outcome in heart transplantation [46-47, 50-51]. The use of other catecholamines does not preclude the use of a heart for transplantation [219-220, 224, 232], especially when their use can be weaned off [225, 240] or when higher doses can be well explained, as outlined above. Note that, whenever novel organ-preservation systems are used, in cases where donor blood is drawn for preservation fluid during procurement for organ transport, then adherence to the manufacturer's recommendation requires adoption of the donor-management protocol.

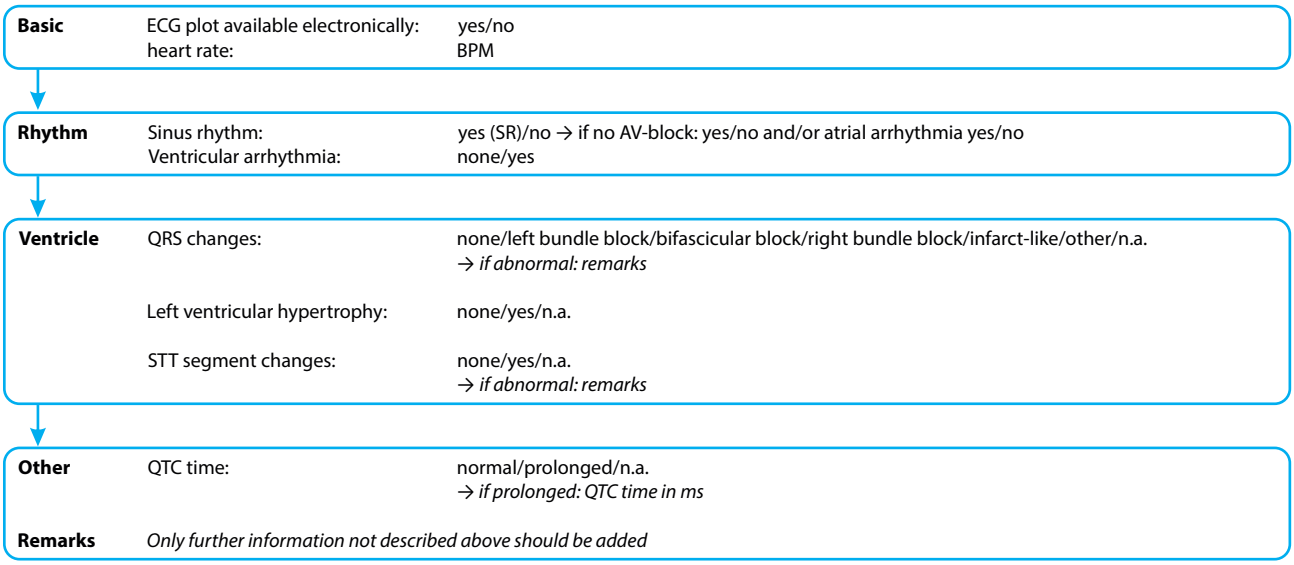
f. *Macroscopic appearance at procurement and perfusion*

Consideration should be given to macroscopic appearance, contractility, wall-motion disorders, coronary artery palpation and morphology of valves or aorta, as well as inspection for other abnormalities (e.g. patent foramen ovale, septal defect).

g. *Other issues*

For organ preservation by cold storage in DBD, planned cold ischaemia times should not exceed 4-5 h (net transport time 2-3 h) without critical consideration of how to manage risks associated with longer ischaemia times in combination with other risk factors as outlined above [221-222, 237]. As well as transport issues affecting the timing of procurement, it is essential to adjust the timing of procurement surgery to the transplant surgery where the

Figure 7.2. **Reporting workflow for minimum dataset to be communicated for electrocardiogram [92]**



n.a. = not assessable.

recipient has had previous heart surgery and/or if removal of an assist device is necessary, due to the severe adhesions likely to be encountered. Using novel organ-preservation technologies may allow an increase in the preservation times above the limits of 4-5 h, by which time confirmative studies have to be completed [222]. Procurement of hearts in DCD and transplantation is currently performed at a limited number of centres in Europe (see Chapter 12). This became successful with introduction of novel organ-preservation technologies including rapid heart procurement with machine resuscitation [244] and thoraco-abdominal normothermic regional perfusion [245].

Concerning recipient parameters, a significant negative impact on patient survival may be observed for the following risk factors: increased age, increased serum creatinine before heart transplant, ventilator dependency, history of diabetes, pulmonary vascular resistance (PVR) exceeding 320 dyn*s*cm^{-5} at heart transplant, previous complex heart surgery, dependency on different cardiac assist devices. Size, weight and gender matches were without significant effect, probably because of adequate donor–recipient matching. Although undersized allografts in recipients with normal/low PVR did not adversely affect survival, in recipients with high PVR this should be avoided because there is clearly defined increased risk [237].

Extending donor criteria to include undersized hearts in recipients without elevated PVR and with gender match may be considered to expand the donor organ pool and reduce mortality rates for patients on the waiting list because, after careful adjustment for all risk factors, mortality seems not to be increased in selected recipients with a donor/recipient weight ratio outside the range < 0.8 to > 1.2 [237, 246].

Currently, criteria for acceptance of ECD hearts for transplantation remain poorly standardised. Future evidence-based research and updated consensus guidelines on ECD donor heart acceptance are necessary, aimed at the

Table 7.2. **Electrocardiogram parameters to be investigated and standard data list**

Electrocardiogram	Comment, informative value
Sinus rhythm QRS-complex ST-segment T-Wave	Sinus tachycardia and supraventricular extra systoles are compatible with brain death. Arrhythmias not related to the acute event of brainstem coning should be excluded. After cerebral damage, QT-elongation, ST-deviation or negative T-waves may temporarily occur. Misinterpretation should be avoided caused by temporary T-Wave and ST-segment changes due to neuro-cardiac damage in direct timely association to the cerebral event. Atrial fibrillation, persisting ventricular extra systoles or QRS deformation, as well as other persisting abnormalities, are indicative of cardiac damage and not only related to a cerebral event. The most recent investigation is most representative.
Hypertrophy	(Left) ventricular hypertrophy should be confirmed by echocardiography.

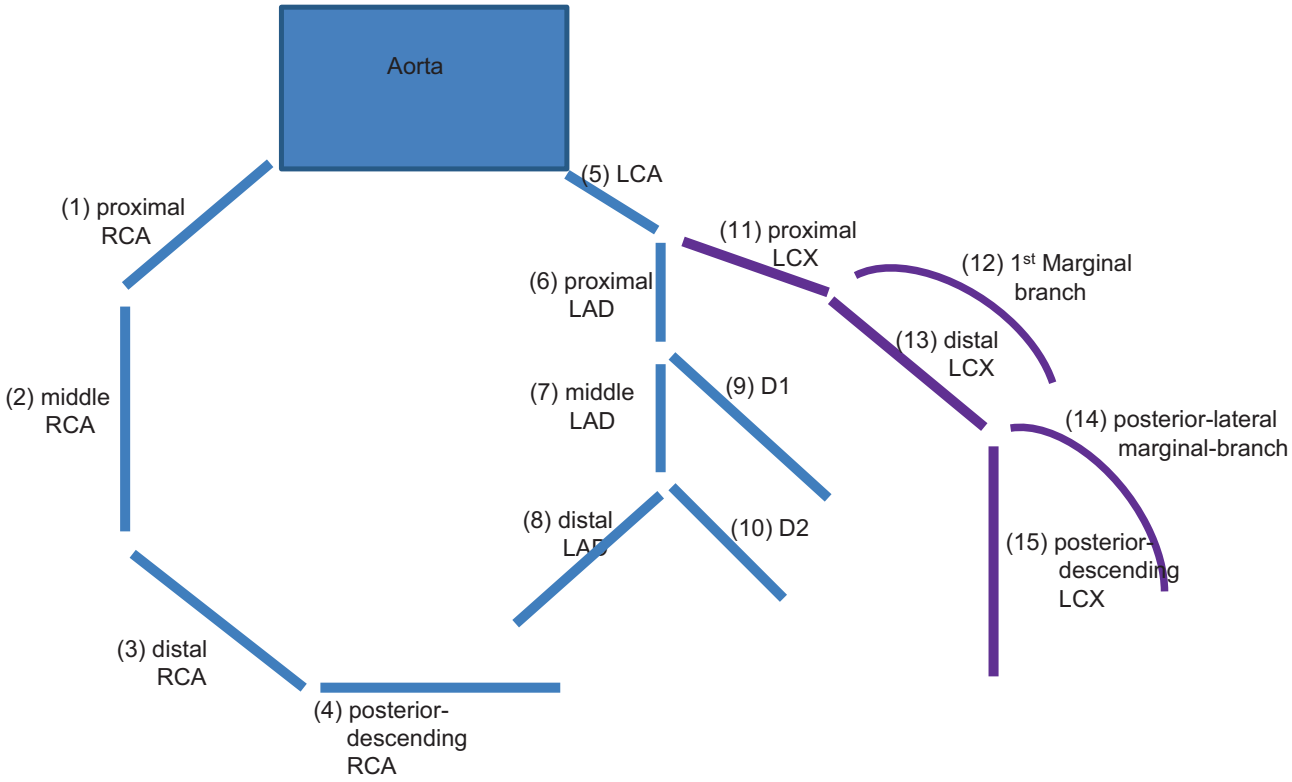
Figure 7.3. **Reporting workflow for minimum dataset to be communicated for echocardiography [92]**

n.a. = not assessable.

Table 7.3. **Echocardiographic parameters to be investigated and standard data list**

Echocardiography	Informative value
Indication	Basic assessment of a heart considered for transplantation as well as haemodynamic status. Transthoracic (TTE) may be sufficient; transoesophageal (TOE/TEE) may be performed if indicated. In donors with tachycardia the heart rate should not be lowered for diagnostic purposes. Sometimes conditions for measurements are limited at bedside at ICU. Haemodynamic status and use of inotropes should be documented.
Right and left heart morphology and function	The function and morphology of all four chambers should be described as outlined in Figure 7.3. Left ventricular hypertrophy is indicative of the quality of treatment for arterial hypertension if other pathologies have been excluded. Good right ventricular function, with hypertrophy due to pulmonary hypertension secondary to lung disease, does not exclude transplantation because many heart recipients suffer from pulmonary hypertrophy. Right ventricular recovery from acute events causing pulmonary hypertension must be demonstrated (e.g. after pulmonary embolism). In elderly donors, slightly impaired diastolic relaxation is a frequent finding due to age-related 'stiffness' of the myocardium.
Regional wall-movement disorders	Exact description is helpful to distinguish between temporary neuro-cardiac injury and other, irreversible damage. Minor movement disorders may not exclude the heart from transplantation – especially if improvement is observed during serial evaluation.
Aortic valve Mitral valve Pulmonary valve Tricuspid valve	Insufficiency of 1st degree is seen often in hearts recovering from acute neuro-cardiac injury in DBD. This does not preclude transplantation. Any insufficiency exceeding 1st degree, stenosis, calcification or other morphologic changes (e.g. increased thickness of a valve leaflet) must be described properly. Pressure- or flow-velocity measurements (e.g. E/E´ or E/A) over the valves are not requested because most donors have tachycardia and measurement will be difficult.
Aortic root and ascending aorta	A dilated aorta is a risk factor for latent aneurysm. Plaques in the ascending aorta are highly susceptible to coronary artery sclerosis.
Pulmonary hypertension	If indicated, estimated (elevated) systolic pulmonary artery pressure should be validated by other methods.
Serial evaluation	Re-evaluations should be performed after haemodynamic stability has been achieved. Functional recovery from reversible neuro-cardiac damage should be assessed in cases of wall-motion abnormalities and/or temporarily impaired left ventricular function.

Figure 7.4. **Coronary arteries and branches**



development of novel and improved methods of donor heart resuscitation and preservation [247] and judiciously increasing utilisation rates, thereby making heart transplantation available to a greater number of patients dying from end-stage heart failure [221-223]. The discrepancies in utilisation rates between countries may be due to differences between transplant centres' willingness to accept 'higher-risk' donor hearts and/or differences in organ procurement organisations' cardiac evaluation and allocation practices.

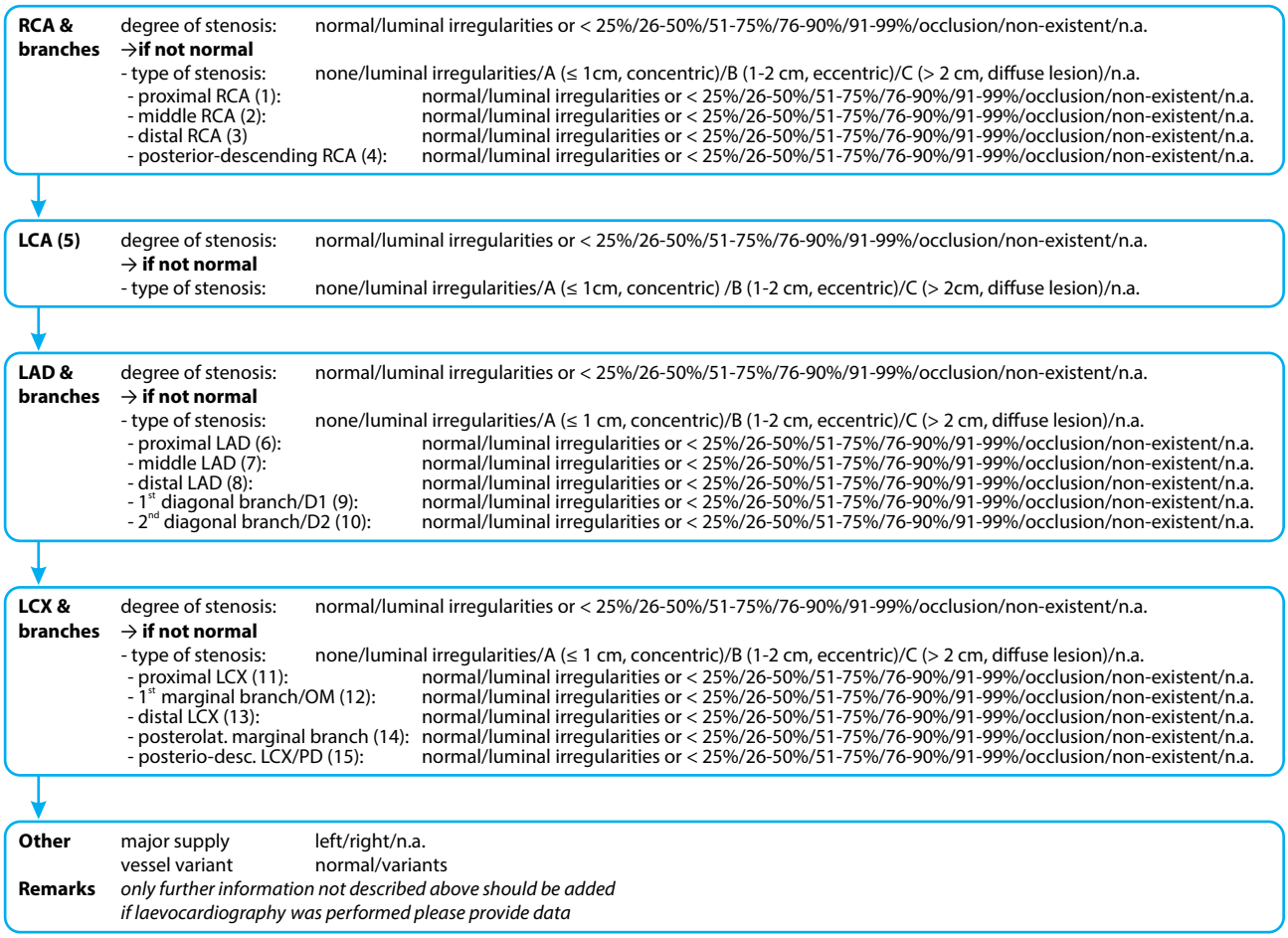
7.2.5.2. *Imaging in the context of heart graft evaluation*

a. *Electrocardiogram*
In any donor an electrocardiogram (ECG, 12-lead measurement at the bedside) may provide additional information as outlined in Table 7.2 (for reporting data, see Figure 7.2 and Appendix 14.4).

b. *Echocardiography*
Echocardiography contributes to bedside assessment of the heart morphology and function (see Table 7.3) and to complementary haemodynamic monitoring. It is imperative to assure that the donor is in the best haemodynamic management condition before assessment by echocardiography if the resulting data are to be valid for the decision whether to use or not use a heart for transplant. In cases of impaired function that can be explained by temporary neuro-cardiac damage, it must be decided whether serial measurements can document recovery of the heart function [228, 248]. A proposal for a standardised dataset to be communicated within the investigation is shown in Figure 7.3 and an example questionnaire can be found in Appendix 14.3.

c. *Coronary angiography*
This invasive investigation should be performed when death has been confirmed and consent for heart procurement exists. Additionally, echocardiography should not have confirmed major damage of the heart [248] and there should be an indication that justifies investigation (see Table 7.4). Also, it should not be assumed that coronary angiography mitigates donor-age-related cardiac risk factors [219, 249]. This investigation assesses the intraluminal status of the coronary vessels (see Table 7.4) and helps the procurement surgeon to rule out palpable plaques, as surrogate for intraluminal stenosis at procurement. Interventions like percutaneous transluminal coronary angioplasty or

Figure 7.5. **Reporting workflow for minimum dataset to be communicated for coronary angiography [92]**



LCA: left coronary artery main stem. LAD: left anterior descending artery. LCX: left circumflex artery. n.a.: not assessable. RCA: right coronary artery.

stenting may only be performed upon agreement with the recipient centre.

A proposal for a standardised dataset to be communicated within the investigation is shown in Figure 7.5 and an example questionnaire can be found in Appendix 14.5. Data of a historic investigation may contribute to verify donor assessment in general. As an alternative to conventional coronary-angiography,

Table 7.4. **Coronary angiography parameters to be investigated and standard data list**

Coronary angiography	Comment, informative value
Indication in donor evaluation	In donors with a heart clinically suitable for transplant but with existing risk for coronary heart disease after all other diagnostics have confirmed suitability: • If donors are aged above 45 years and if there is a significant risk of coronary artery disease (CAD), e.g. all male donors over the age of 55 (with or without risk factors for CAD) or females aged over 55 with one or more risk factors for CAD, and donors of either sex aged between 45 and 55 years if more than one risk factor for CAD exists. • Complications may occur during transfer and investigation (e.g. donor instability, worsening of lung function, vasospasm with cardiac arrest, rupture of vessel).
Coronary sclerosis and stenosis	The narrowing and shape of stenosis, its location and affection of the vessel should be described, as well as the shape of the intravascular structure of RCX, LCX, LCA, RIVA and their branches. In cases of a stenosis detected during investigation, interventions like PTCA or stenting may be done only upon agreement by the recipient centre.
Facultative laevocardiography	Functional parameters can be obtained if appropriate echocardiography is not available and if investigation of coronary vessels is indicated anyway (e.g. aortic valve, LVEF, LVEDV, LVEDP, LV-wall motion abnormalities, LV-hypertrophy).

n.a. = not assessable.

CT- coronary-angiography may be considered if technically possible due to donor tachycardia.

7.2.6. Lung-selection criteria

7.2.6.1. *Issues in lung selection*

a. *Age*
This criterion depends on individual donor/recipient evaluation and individual transplant team assessments. Experienced centres have increased the upper age limit for routine lung donation to 80 years [1, 250]. In advanced-age donors, some limiting factors such as pleural adhesions, micro-emphysema or apical scars can only be ruled out by intra-operative inspection at procurement. At least in every donor younger than 80 with a PaO_2/FiO_2 of > 250 mmHg, lung donation should be considered after proper assessment and recruitment of atelectasis.

b. *Past and current medical history*
A history of pulmonary disease, active pulmonary infection, aspiration, purulent secretions, thoracic trauma and previous thoracic surgery are considered as risk factors for inferior outcomes after transplantation. Regarding the history of smoking expressed in pack-years, probably no limitations exist when smoking-related co-morbidities are ruled out (e.g. increased risk of malignancy, chronic inflammation/infection). Other chronic lung diseases without structural damage to the lung parenchyma require a case-by-case decision (e.g. asthma, micro-emphysema). Lung grafts will not be used in cases of tuberculosis or chronic obstructive lung disease (COPD).
Acute deterioration of gas exchange with PaO_2/FiO_2 < 250 mmHg (< 33.3 kPa) with positive end expiratory pressure (PEEP) = 5 cmH_2O requires a careful work-up. When recovery from trauma/contusion, aspiration, inappropriate ventilation, fever, fluid overload or transfusion-associated lung injury can be demonstrated, then lungs can be used for transplantation.
It is well known that a series of injuries occurs in the donor lung from the time of devastating cerebral injury, during brain-stem coning, death declaration, preservation and transplantation until reperfusion in the recipient, which may cause primary graft dysfunction with recipient mortality [251-254]. Minimising such risks by adequate donor selection and management is critical.
The major concern when considering lung donors with a history of smoking is the potential for poor lung function due to an obstructive pulmonary disease and the risk of an undetected primary or metastatic cancer [254-256]. In some studies smoking history in lung donors is associated with decreased recipient survival [257], but this is still higher than when remaining on the waiting list [258]. Other studies could not confirm a relevant impact on long-term survival [253, 259-261]. Therefore a donor history of smoking should not prevent the use of lungs for transplantation when no objective risks exist.
Post-transplantation pneumonia and sepsis are serious concerns. Prospective analysis of donor airway cultures and bronchial tissue cultures revealed a < 1.5 % transmission rate of donor organ contamination [262-263]. Positive donor Gram stain did not predict post-transplant pneumonia, oxygenation or duration of post-transplant mechanical ventilation [264-267]. The Newcastle group reported decreased survival in a group of patients with positive cultures of donor broncho-alveolar lavage (BAL), suggesting that lower airway colonisation may be indicative of an increased risk for post-operative graft infection and dysfunction [268]. Therefore, the impact of microbial colonisation or subclinical infection in assessing the donor lung is not completely clear but important. Successful transplantation is possible with frequent post-operative microbial airway sampling and adequate antibiotic treatment against the identified organisms.
Potential donors on mechanical ventilation for prolonged periods are at increased risk of ventilator-associated pneumonia. It has been found that duration of donor ventilation correlates strongly with the presence of infection. In one study, 90.5 % of donors ventilated for more than 48 h were infected [269]. But in another study no increased rates of recipient infections with organisms identified in the donor lung were observed with donor lungs ventilated for up to 15 days after the initial intubation [270]. There is no evidence that donors should be excluded solely on the basis of the length of mechanical ventilation. At the time of writing, lungs of donors who test positive for SARS-CoV-2 are not being offered for transplantation (see §8.6.2.19).

c. *Gas exchange*

This should be assessed in order to exclude organs with inadequate gas exchange. A functional challenge test of gas exchange is the coupled measurement of the blood gases at baseline 1.0 FiO_2 at a minimum PEEP of 5.0 cm H_2O, and temporarily increment to 1.0 FiO_2 for 10 minutes. For this measurement, bronchial cleaning and recruitment of atelectasis must be performed in advance. The aim of this test is to identify the quality of gas exchange. Lungs should not be excluded for low PaO_2/FiO_2 until at least 2 h of adequate treatment (which includes protective mechanical ventilation, recruit manoeuvres and bronchoscopy to remove clots and sputum and improve lung function) has been given. Diuretics have been applied if there is low PaO_2/FiO_2 and pulmonary oedema, evaluated by extravascular lung water index > 10 ml/kg, if PICCO® or a similar monitor is used, or central venous pressure over 10 cm of water (see Chapter 5) [271].

Donors with persisting reduced lung function can still be considered for single lung donation at procurement after evaluation of gas exchange in individual lungs on a blood sample taken in the pulmonary veins. Many centres ask for acute ventilator settings and for data about all microbiological investigations, e.g. tracheal suction or BAL sent in for investigation in order to know which pathogens are in the graft.

Arterial partial pressure of oxygen (PaO_2) is a tool for assessing lung function. The PaO_2/FiO_2 ratio can be easily affected by reversible processes such as retained secretions, pulmonary oedema and atelectasis. Several authors have shown that initial PaO_2/FiO_2 < 300 mmHg after brain death diagnosis does not make the donors ineligible for lung donation. Indeed, the initial PaO_2/FiO_2 can increase by nearly 100 mmHg with adequate treatment (see Chapter 5). In more than one-third of lung donors with low PaO_2/FiO_2, that would otherwise have not been considered for donation, oxygenation value was increased over 300 mmHg and the lungs were finally transplanted without impact on the recipient's survival [271-272]. Donor management for improving initially poor gas exchange is important (see Chapter 5). Steroid administration after brain death is associated with an increase in PaO_2/FiO_2 [235-236].

d. *Morphological examinations*

Chest X-ray is mandatory to rule out major pathologies (e.g. space-occupying lesions, structural changes of lung parenchyma) and, if indicated, a CT scan is preferred [273]. Bronchoscopy is performed at an ICU for primary assessment (and cleaning of airways if necessary) as well as by the procurement teams for final assessment (for diagnostic reasons as well as to perform better intra-tracheal cleaning). Recovery from lung contusions should be considered after effective ventilator therapy for a few days. (For details of the set of investigations, see §7.2.6.2.)

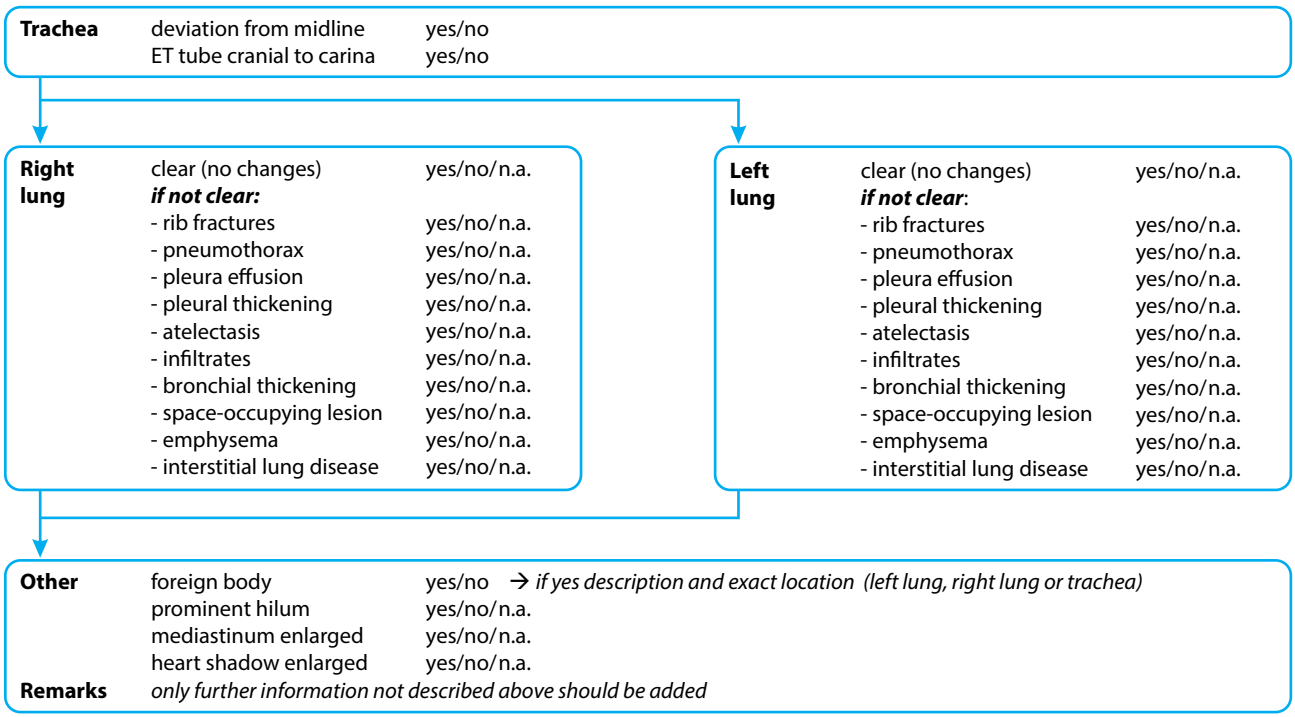
Donors undergo multiple chest radiographs, after their admission to ICU, until procurement. In a retrospective survey, one third of all donor radiographs had infiltrates, which improved or resolved spontaneously in more than 50-80 % of cases [274-275]. All patients transplanted with such infiltrates were alive after one year of follow-up. Plain chest X-rays taken at the bedside are of low sensitivity and only CT scans can properly estimate structural abnormalities like minor contusions or small infiltrates. Indeed, lungs should not be rejected because of minor abnormalities observed in CT scan, because a CT scan is too sensitive; most of these abnormalities could be reversed with proper treatment and they do not have a negative influence on recipients' outcome [276]. Donors with strong unilateral abnormalities should not be excluded for donation of the contralateral lung [277]. Finally, evaluation of a donor chest X-ray is highly subjective, which limits its value for determining organ suitability [278]. No studies have been found that correlate chest radiograph findings and recipient infections.

e. *Improvement of lung function by donor management*

As outlined in Chapter 5, proper management of the donor improves lung function and allows many grafts to be resuscitated and used for transplantation. Whenever disconnection of the donor from the ventilator at the ICU occurs, then (after reconnection at the ICU) recruitment manoeuvres should be considered to re-improve lung function [279]. Unnecessary disconnections should be avoided.

Brain-death-induced lung injury may be explained by an initial excessive increase in pulmonary capillary pressure with increased

Figure 7.6. **Reporting workflow for minimum dataset to be communicated for X-ray of chest/thorax or computed tomography of thorax [92]**



ET: endotracheal. n.a: not assessable.

pulmonary venous resistance. This is associated with activation of inflammatory apoptotic processes which can be prevented by use of methylprednisolone [254].

f. *Macroscopic appearance at procurement*
Consideration should be given to the colour of the lungs, presence of atelectasis, tumours, water content of the tissue, contusion marks, signs of early pneumonia, appropriate insufflations and pleural adhesions. Single-lung transplantation is possible for selected recipients in the case of one lung being unsuitable. Sometimes pneumonia, structural changes or apical scars may not be detected until procurement surgery. Recruitment of atelectasis can be done under *in situ* control and care of the lung surgeon, in collaboration with the anaesthesiologist, in order to avoid barotrauma. Selective blood-gas analysis of the pulmonary veins helps to identify areas with good or impaired gas exchange (especially when the global arterial PaO_2/FiO_2 is below 250 mmHg or 33.3 kPa). Resection of compromised lung areas is at the discretion of the procurement team and recipient centre. The same procedure can be considered for size adaptation of oversized lungs or areas of localised emphysema.

g. *Other issues*
Lungs can be successfully transplanted from both uncontrolled and controlled DCD donors [1, 280-282]. See Chapter 12.
Single-lung donation should always be considered when one lung is deemed unsuitable.
Ex situ lung perfusion is a new technique, used to safely extend the cross-clamp time [283] and to evaluate high-risk donor organs [284], that allows careful visual inspection of the explanted lungs: reventilated and blood reperfused for functional assessment with measurement of gas exchange, haemodynamic and aerodynamic parameters, and indicators of lung oedema. Many studies have demonstrated similar length of mechanical ventilation, rate of primary graft dysfunction, length of stay and mortality [285-290]. Dramatic changes in lung-selection criteria must be expected in the future by use of *ex situ* lung perfusion and growing experience in repairing damaged grafts [244].

Table 7.5. **Bronchoscopy parameters to be investigated and standard data list**

Bronchoscopy	Comment, informative value, background
Indication	In a potential lung donor before procurement or for exclusion of bronchial malignancy if suspected, or for cleaning airways to improve gas exchange and pulmonary function (especially after suspected aspiration).
Status of bronchus and trachea	Blocked peripheral orifices or purulent secretions may indicate infection (pneumonia). Bleeding or ulceration may have multiple causes; consider additional chronic inflammation due to smoking history. Any tumour detected requires histology prior to transplantation of any organ. Secretions originating from the peripheral bronchial orifice indicate infection in peripheral tissue of the lung (purulent, blood, clean). Samples should be sent to microbiology for identification of colonisation or infection (e.g. bacteria or fungi and their resistance pattern against anti-microbiological agents).

7.2.6.2. *Imaging in the context of lung graft evaluation*

a. *X-ray thorax*
Chest X-ray can be performed as a bedside method in the ICU with the known limitations of the sensitivity and specificity of the investigation. A proposal for a standardised dataset to be communicated within the investigation is shown in Figure 7.6; an example questionnaire can be found in Appendix 14.1. Small space- occupying lesions or minor changes of the parenchymal structure may not be detected. Lung size measurement is not required for standard matching of donor and recipient (exception: malformations of the thoracic cavity of the potential recipient or in extremely adipose donors). The investigation should not be outdated (e.g. older than 4-8 h).
Whenever a whole-body CT scan or thoracic CT scan or magnetic resonance imaging (MRI) has been performed, re-evaluation should be attempted for donation purposes. Beyond investigation for space-occupying lesions, the data can be entered into the same grid as suggested for chest X-ray. In donors with a previous history of malignancy, it is highly recommended to perform a whole-body CT scan according to the recommendations of Chapter 9.

b. *Bronchoscopy*
Bronchoscopy can be performed as a bedside method especially for assessing the status of the bronchial system (see Table 7.6). A proposal for a standardised dataset to be communicated within the investigation is shown in Figure 7.7 and an example questionnaire can be found in Appendix 14.2. If performed, the investigation should not be older than eight hours for assessment of lung quality. Many lung procurement teams re-perform bronchoscopy during procurement.

c. *Computer tomography or magnetic resonance imaging of the thorax*
Whenever a whole-body CT scan or thoracic CT scan or MRI has been performed, re-evaluation should be attempted for donation purposes. These investigations can provide additional information on the issues outlined in Table 7.6. Note that a pre-procurement CT scan helps to identify suspect space-occupying lesions at an earlier stage, which may also help to exclude malignancies [93] and reduce risk by the detection of unspecific lesions, as well as providing additional information on anatomical variants. The indication for this method is a controversial subject of discussion in various European countries (see §6.7).

7.2.7. Vascularised composite allografts

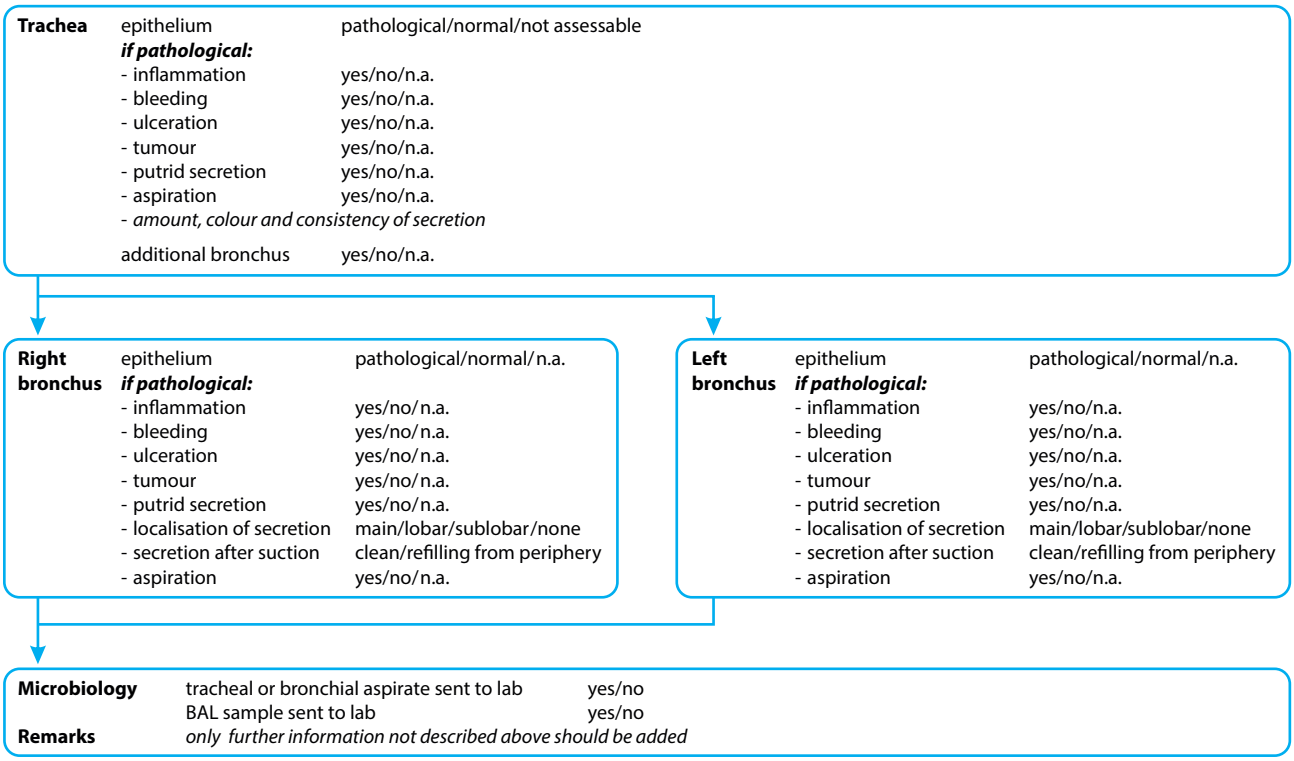
Vascularised composite allografts (VCAs) are defined as heterogeneous tissues containing skin, muscles, bones, tendons and vessels, requiring surgical connection of blood vessels and nerves for allograft function. All the issues of VCAs in the donation process are discussed in detail in Chapter 15.

VCAs are subject to the same time constraints as organs due to their vulnerability to ischaemia, the absence of storage options and the need for immunosuppressive therapy. Among VCAs, hand, forearm and facial transplantations have progressed. Currently, experience is limited to a few transplant centres.

7.2.8. Tissue- and cell-specific selection criteria

Please refer to the latest edition of the Council of Europe *Guide to the quality and safety of tissues and cells for human application*. These criteria differ from organ criteria, among other reasons because no one-to-one relationship exists between donor and recipient (allocation schemes are different) and because tissues and cells are processed further. Whenever organs (e.g. heart, pancreas) are assessed as unsuit-

Figure 7.7. **Reporting workflow for minimum dataset to be communicated for bronchoscopy [92]**



BAL: broncho-alveolar lavage. n.a: not assessable.

able for transplantation before or during organ procurement, the use of these organs to obtain tissues/cells for human application should be considered (e.g. heart valves, islets). This will require *ad hoc* collaboration with tissue/cell donation experts.

7.3. Donor and organ documentation

This issue is discussed in Chapter 6. Within the donor selection and organ-specific selection processes it is helpful to document clearly the reasons for each decision, based on the data levels recorded for the donor and/or organ being unacceptable, being either not suitable for any patient or not suitable for a particular donor–recipient combination. Only exact data about such decisions will allow future improvements in donor-selection criteria while monitoring transplant outcomes (see Chapter 17).

7.4. Immunological considerations

The interaction between the recipient's immune system and the transplanted graft is a challenging issue, because acute or chronic rejections are the endpoint of this and they cause transplantation failure.

Note that, in DBD, the pathophysiological changes cause a systemic inflammatory response syndrome (SIRS), which is treated by aggressive donor management (see Chapter 5) but still causes upregulation of many cellular receptors or pathways in the context of inflammation. After reperfusion of the graft in the recipient, ischaemia reperfusion injury (IRI) occurs as soon as the recipient's immune system is in contact with it for the first time. To avoid rejection events the recipient's immune system is suppressed. Unfortunately the side effects of previous immunisations (especially in the HLA system) cannot be eliminated. From this point of view, safety precautions become necessary but these have an impact on:

- the individual decision whether to use a particular graft in one recipient or not,
- other decisions on the diagnostics or procedures that are needed to decrease the risks for a recipient beyond the scope of data outlined in this guide and any other medical issues in the recipient.

The appropriate amount of diagnostics is discussed in section 6.6 on HLA-typing of the donor and matching or cross-matching procedures (virtual or based on laboratory examinations) to reduce the risks for recipients. The impact of the recipient's sensitisation and the turnaround time for diagnostics, as well

Table 7.6. **Computer tomography or magnetic resonance considerations in thoracic donor evaluation**

CT-thorax	Comment, informative value
Heart/vessels	Identification of trauma or haematoma and description of coronary vessels are possible by angio-CT if coronary angiography is impossible and if donor tachycardia is not limiting technically.
Lung	Check for smaller tumours and abnormal lymph nodes to exclude malignancies and pneumonitis. Highly sensitive for effusion, pneumonia, atelectasis, pneumothorax, embolism and vessel alterations as well as structural abnormalities. Pulmonary contusion: restorations possible after a prolonged time interval (days).

as consideration about backup recipients, determine the range of acceptance criteria. In such cases there is increased risk of exposing the graft to prolonged ischaemia times. In this context it is highly recommended to consider non-sensitised backup recipients in case of primary graft allocation to a recipient who is highly sensitised against HLA with the need of pre-implantation diagnostics. Unfortunately this pragmatic issue is not well discussed in the literature, although consensus guidelines exist for managing a recipient with such HLA sensitisation [68, 291]. Reintroduction of some kind of HLA-matching in elderly recipients receiving grafts from elderly donors within special programmes (e.g. Eurotransplant Senior Program) might mitigate the complications of rejection [20] beyond the issue that this sub-population is exposed to different immunological risks [21].

7.5. Conclusion

Appropriate donor and organ characterisation contributes to the safety and quality of organs used for transplantation. It has to be remembered that certain medical findings are indicative for accepting or discarding a particular organ, e.g. severe macro-vesicular steatosis of the liver, even though other grafts of the same donor can be transplanted without increased risk. Some other donor factors cannot be eliminated or avoided and therefore persist as risk factors after transplantation (e.g. donor age). The aim of donor and organ characterisation is to ensure adequate allocation of the organ to the recipient with the highest probability of benefit from a transplant, based on the data acquired during the process as outlined.

Organ donation and transplantation are procedures carried out within significant time constraints, especially in deceased organ donation, where most procedures are rapidly carried out to keep ischaemic times as short as possible while adhering to formal and legal requirements.

Risk evaluation of donor and recipient factors is carried out on an individual, case-by-case basis. There may be factors that make a given organ from a donor absolutely unsuitable for a specific recipient, whereas the same organ could be life-saving for another recipient. This is why there are only a few absolute contraindications against organ donation. Current boundaries are even further challenged when there is urgency for transplantation among the increasing number of potential recipients on the waiting list. It is the duty of the transplant physician to carefully evaluate donor and recipient factors in an individual risk–benefit analysis, while it is a shared general responsibility of the authorities in charge, and of the medical community, to organise transplant systems (including allocation schemes) in such a way that organ loss is prevented and organs donated are respected to the highest possible extent. By the same philosophy, it is important to document and assess when and why organs procured were finally not used, to learn from these findings and ensure optimised organ use for the future.

A customised donor/organ profile of each patient enrolled on the transplant waiting list may facilitate planning of adequate donor/recipient risk assessments and the best use of all suitable organs.

Finally, the team of physicians performing the transplantation have the overall responsibility for its use in that particular recipient, regardless of the considerations and risks in donor and organ selection as presented above.

Questions for future research have been summarised below.

Research agenda

From the literature and discussion of the available evidence, several topics have been identified for which evidence is inconsistent, insufficient or non-existent. The authors of this guide recommend that future research, where possible in well-designed randomised clinical trials, should focus on the following research gaps and key questions for each organ:

1 Donor age: Is there an impact from donor age in very young as well as very old donors? Can we expect an interaction with other factors?
2 Past and current medical history: Which current acute events compromise the graft quality after transplantation? Which events in the medical history compromise graft quality after transplantation?
3 Graft function parameters: Do imaging or laboratory

or other data allow a prognosis about the issues covered by 1 and 2?
4 Imaging pre-procurement: What information should a diagnostic test provide?
5 Morphologic assessment at procurement: Are there any factors that allow a prognosis of the issues covered by 1 and 2?
6 Biopsy: Are there any factors that provide prognostic information that might inform a decision to use an organ?
7 Other issues: Which other various factors should be considered about a prognosis of the issues covered by 1 and 2?
8 Modifications by donor management: Can we modify the impact of some risk factors mentioned above by intensive care therapy?
9 Recipient-related issues: What recipient factors, in general, compromise outcome? What combination of donor and recipient factors improves outcome or compromises outcome (based on the fact that we only have elderly donors with co-morbidities as reference point)? What about immunological factors causing problems after implantation by the immune system of the new host?
10 Interaction of factors above: What interaction exists between the above-mentioned topics?

The organ-specific selection criteria will be reviewed on the basis of the above questions.
Note that the research proposed above is basic work that is assumed to be of low prestige but that needs to be done in order to overcome existing assumptions when excluding organs, assumptions which may be correct or incorrect in view of the conflicting reports in the literature. This research requires consideration of multiple interacting variables of donors and recipients [110, 219, 224] as well as novel preservation or assessment technologies [193, 244, 292-293].

7.6. References

1. Andrés A, Fischer-Fröhlich CL. Chapter 4: Organ viability. In: Valero R, ed. *Transplant coordination manual*. 3rd edition, pp. 99-154. Barcelona: Aguiló-grafic, 2014. ISBN: 978-84-616-8840-1.
2. Panis Y, Massault P, Sarfati P *et al.* Emergency liver retransplantation using a polycystic donor liver. *Transplantation* 1994;57:1672-3.
3. Jiménez C, Moreno E, García I *et al.* Successful transplantation of a liver graft with a calcified hydatid cyst after back-table resection. *Transplantation* 1995;60: 883-4.
4. Mor E, Bozzagni P, Thung SN *et al.* Backtable resection of a giant cavernous hemangioma in a donor liver. *Transplantation* 1995;60:616-17.
5. Moreno E, García I, González-Pinto I *et al.* Successful reuse of a liver graft. *Br J Surg* 1991;78:813-14.
6. Rentsch M, Meyer J, Andrassy J *et al.* Late reuse of liver allografts from brain-dead graft recipients: the Munich experience and a review of the literature. *Liver Transpl* 2010;16:701-4.
7. Pasic M, Gallino A, Carrel T *et al.* Reuse of a transplanted heart. *N Engl J Med* 1993;328:319-20.
8. Fischer-Fröhlich CL, Königsrainer A, Schaffer R *et al.* Organ donation: when should we consider intestinal donation? *Transpl Int* 2012;25:1229-40.
9. Andrés A, Morales JM, Herrero JC *et al.* Double versus single renal allograft from aged donors. *Transplantation* 2000;69:2060-6.
10. Pérez-Sáez MJ, Montero N, Redondo-Pachón D *et al.* Strategies for an expanded use of kidneys from elderly donors. *Transplantation* 2017;101:727-45.
11. Balachandran V, Aull M, Goris M *et al.* Successful transplantation of single kidney from pediatric donors weighing less than or equal to 10 kg into standard weight adult recipients. *Transplantation* 2010;90:518-22.
12. Gallinat A, Sotiropoulos GC, Witzke O *et al.* Kidney grafts from donors ≤ 5 yr of age: single kidney transplantation for pediatric recipients or en bloc transplantation for adults. *Pediatr Transplant* 2013;17: 179-84.
13. Maluf DG, Carrico RJ, Rosendale JD *et al.* Optimizing recovery, utilization, and transplantation outcomes for kidneys from small, ≤ 20 kg, pediatric donors. *Am J Transplant* 2013;13:2703-12.
14. Laurence JM, Sandroussi C, Lam VW *et al.* Utilization of small pediatric donor kidneys: a decision analysis. *Transplantation* 2011;91:1110-13.
15. Giessing M. Ten years of the Eurotransplant senior program: are there still age limits for kidney transplantation? *Urologe* A 2009;48:1429-37.
16. Giessing M, Fuller TF, Friedersdorff F *et al.* Outcomes of transplanting deceased-donor kidneys between elderly donors and recipients. *J Am Soc Nephrol* 2009; 20:37-40.
17. Lledó-Garciá E, Riera L, Passas J *et al.* Spanish consensus document for acceptance and rejection of kidneys from expanded criteria donors. *Clin Transplant* 2014;28:1155-66.
18. Tanriover B, Mohan S, Cohen DJ *et al.* Kidneys at higher discard: expanding the role of dual kidney transplantation. *Am J Transpl* 2014;14:404-15.
19. Gallinat A, Feldkamp T, Schaffer R *et al.* Single-center experience with kidney transplantation using deceased donors older than 75 years. *Transplantation* 2011 Jul 15;92(1):76-81.
20. Dreyer G, Fijter J. Transplanting the elderly: mandatory age- and minimal histocompatibility matching. *Front Immunol*, 2020;11:359. https://doi.org/10.3389/fimmu.2020.00359.
21. Noble J, Jouve T, Malvezzi P *et al.* Transplantation of marginal organs: immunological aspects and

therapeutic perspectives in kidney transplantation. *Front Immunol* 2019;10:3142. https://doi.org/10.3389/fimmu.2019.03142.

22. Cecka JM, Terasaki PI. Optimal use for older donor kidneys: older recipients. *Transplant Proc* 1995;27:801-2.
23. Herrero JC, Gutiérrez E, Martínez A *et al.* Results of kidney transplantation in recipients over 70 years of age: experience at a single center. *Transplant Proc* 2003;35:1675-6.
24. Remuzzi G, Cravedi P, Perna A *et al.* Long-term outcome of renal transplantation from older donors. *N Engl J Med* 2006;354:343-52.
25. Andrés A, Hernandez A, Herrero JC *et al.* Kidney transplant in extremely aged recipients using extremely aged deceased donors [abstract]. *Am J Transplant* 2008;8(Suppl 2):455.
26. Nyengaard JR, Bendtsen TF. Glomerular number and size in relation to age, kidney weight and body surface in normal man. *Anat Rec* 1992;232:194-201.
27. Denic A, Lieske J, Chakkera H *et al.* The substantial loss of nephrons in healthy human kidneys with aging. *J Am Soc Nephrol* 2017;28:313-20.
28. Echterdiek F, Schwenger V, Döhler B *et al.* Kidneys from elderly deceased donors – is 70 the new 60? *Front Immunol* 2019;10:2701. https://doi.org/10.3389/fimmun.2019.02701.
29. Lim WH, Chang S, Chadban S *et al.* Donor–recipient age matching improves years of graft function in deceased-donor kidney transplantation. *Nephrol Dial Transplant* 2010;25:3082-9.
30. The Canadian Council for Donation and Transplantation. *Kidney allocation in Canada: a Canadian forum, report and recommendations (Toronto, ONT, Canada, 2006).* Edmonton AB, Canada: Canadian Council for Donation and Transplantation, 2007, available at https://profedu.blood.ca/en/organs-tissues/transplantation/leading-practices-and-clinical-guidelines/kidney-allocation, accessed 16 May 2021.
31. Wang J, Skeans M, Israni A. Current status of kidney transplant outcomes: dying to survive. *Adv Chronic Kidney Dis* 2016;23:281-6.
32. Aubert O, Kamar N, Vernerery D *et al.* Long term outcomes of transplantation using kidneys from expanded criteria donors: prospective, population based cohort study. *BMJ* 2015;351:h3557.
33. Savoye E, Macher MA, Videcoq M *et al.* Evaluation of outcomes in renal transplantation with hypothermic machine perfusion for the preservation of kidneys from expanded criteria donors. *Clin Transplant* 2019;33:e13536.
34. Arcos E, Pérez-Sáez M, Cornas J *et al.* Assessing the limits in kidney transplantation: use of extremely elderly donors and outcomes in elderly recipients. *Transplantation* 2020;104(1):176-83.
35. Port FK, Bragg-Gresham JL, Metzger RA *et al.* Donor characteristics associated with reduced graft survival: an approach to expanding the pool of kidney donors. *Transplantation* 2002;74(9):1281-6.
36. Metzger RA, Delmonico FL, Feng S *et al.* Expanded criteria donors for kidney transplantation. *Am J Transplant* 2003;3(Suppl 4):114-25.
37. Becker YT, Leverson GE, D'Alessandro AM *et al.* Diabetic kidneys can safely expand the donor pool. *Transplantation* 2002;74(1):141-5.
38. Ojo AO, Leichtman AB, Punch JD *et al.* Impact of pre-existing donor hypertension and diabetes mellitus on cadaveric renal transplant outcomes. *Am J Kidney Dis* 2000;36:153-9.
39. CKD Work Group. Kidney disease: improving global outcomes. KDIGO 2012 Clinical practice guideline for the evaluation and management of chronic kidney disease. *Kidney Int* 2013;89(Suppl 3):1-150, available at https://kdigo.org/guidelines/ckd-evaluation-and-management/, last accessed 15 May 2021.
40. Molina M, Apaza J, González Monte E *et al.* Results of kidney transplantation from deceased donors with acute kidney injury. *Transplant Proc* 2015;47:42-4.
41. Anil Kumar MS, Khan SM, Jaglan S *et al.* Successful transplantation of kidneys from deceased donors with acute renal failure: three-year results. *Transplantation* 2006;82(12):1640-45.
42. Rodrigo E, Miñambres E, Piñera C *et al.* Using RIFLE criteria to evaluate acute kidney injury in brain-deceased kidney donors. *Nephrol Dial Transplant* 2010;25:1531-7.
43. Liu C, Hall I, Mansour S *et al.* Association of deceased donor acute kidney injury with recipient graft survival. *JAMA Network Open* 2020;3:e1918634. DOI: 10.1001/jamantetworkopen.2019.18634.
44. Bauer J, Grzella S, Bialobrzecka M *et al.* Success of kidney transplantation from deceased donors with acute kidney injury. *Ann Transplant* 2018;23:836-44.
45. Carvalho de Matos AC, Requião-Moura LR, Clarizia G *et al.* Expanding the pool of kidney donors: use of kidneys with acute renal dysfunction. *Einstein (Sao Paulo)* 2015;13:319-25.
46. Benck U, Hoeger S, Brinkkoetter PT. Effects of donor pretreatment with dopamine on survival after heart transplantation: a cohort study of heart transplant recipients nested in a randomized controlled multicenter trial. *J Am Coll Cardiol* 2011;58:1768-77.
47. Richmond ME, Easterwood R, Singh RK *et al.* Low-dose donor dopamine is associated with a decreased risk of right heart failure in pediatric heart transplant recipients. *Transplantation* 2016;100:2729-34.
48. Schnuelle P, Gottmann U, Hoeger S *et al.* Effects of

donor pretreatment with dopamine on graft function after kidney transplantation: a randomized controlled trial. *JAMA* 2009;302:1067-75.

49. Schnuelle P, Schmitt HS, Weiss C *et al.* Effects of dopamine donor pretreatment on graft function after kidney transplantation: a randomized trial. *Clin J Am Soc Nephrol* 2017;12:493-501.
50. Brinkkoetter PT, Song H, Lösel R *et al.* Hypothermic injury: the mitochondrial calcium, ATP and ROS love–hate triangle out of balance. *Cell Physiol Biochem* 2008;22(1-4):195-204.
51. Schnuelle P, Benck U, Yard BA. Dopamine in transplantation: write off or comeback with novel indication? *Clin Transplant* 2018;32:e13292.
52. Yard B, Beck G, Schnuelle P *et al.* Prevention of cold preservation injury of cultured endothelial cells by catecholamines and related compounds. *Am J Transplant* 2004;4:22-30.
53. Malinoski D, Patel M, Axelrod D *et al.* Therapeutic hypothermia in organ donors: follow-up and safety analysis. *Transplantation* 2019;103:e365-e368.
54. Amenábar JJ, Camacho JA, Gómez-Larrambe N *et al.* Prognostic utility of preimplantation kidney biopsy from deceased older donors in first year post-transplant renal function. *Nefrologia* 2016;36:33-41.
55. Sofue T, Inui M, Kiyomoto H *et al.* Pre-existing arteriosclerotic intimal thickening in living-donor kidneys reflects allograft function. *Am J Nephrol* 2012;36:127-35.
56. Kasiske BL, Stewart DE, Bista BR *et al.* The role of procurement biopsies in acceptance decisions for kidneys retrieved for transplant. *Clin J Am Soc Nephrol* 2014; 9:562-71.
57. Pisarski P, Schleicher C, Hauser I, Becker JU. German recommendations for pretransplant donor kidney biopsy. *Langenbecks Arch Sur,* 2016;401:133-40.
58. Woodside KJ, Merion RM, Leichtman AB *et al.* Utilization of kidneys with similar kidney donor risk index values from standard versus expanded criteria donors. *Am J Transpl* 2012;12:2106-14.
59. Bae S, Massie AB, Luo X *et al.* Changes in discard rate after introduction of the kidney donor profile index (KDPI). *Am J Transpl* 2016;16:2202-7.
60. Wang CJ, Wetmore JB, Cray CS, Kasieke BL. The donor kidney biopsy and its implications in predicting graft outcome: a systematic review. *Am J Transpl* 2015; 15:1903-14.
61. Reese P, Harhay M, Abt P *et al.* New solutions to reduce discard of kidneys donated for transplantation. *J Am Soc Nephrol* 2016;27:973-80.
62. Phillips B, Kassimatis T, Atalar K *et al.* Chronic histological changes in deceased donor kidneys at implantation do not predict graft survival: a single center retrospective analysis. *Transpl Int* 2019;32:523-34. DOI:10.1111/tri.13398.
63. Liapis H, Gaut JP, Klein C *et al.* Banff histopathological consensus criteria for preimplantation kidney biopsies. *Am J Transpl* 2017;17:140-50.
64. Salvadori M, Tsalouchos A. Histological and clinical evaluation of marginal donor kidneys before transplantation: which is best? *World J Transplant* 2019;9: 62-80.
65. Mohan S, Cheiles M, Patzer R *et al.* Factors leading to the discard of deceased donor kidneys in the United States. *Kidney Int* 2018;94:187-98.
66. Stallone G, Grandaliano G. To discard or not to discard: transplantation and the art of scoring. *Clinical Kidney J* 2019;12:564-8.
67. Angeletti A, Cravedi P. Making procurement biopsies important again for kidney transplant allocation. *Nephron* 2019;142:1-6.
68. Abramowicz D, Cochat P, Claas F *et al.* European renal best practice guideline in kidney donor and recipient evaluation and perioperative care. *Nephrol Dial Transplant* 2013;28(Suppl 2):ii1-ii71.
69. Portolés J, Marañes A, Prats D *et al.* Double renal transplant from infant donor. *Transplantation* 1996; 61:37-40.
70. Kirste G, Blümke M, Krumme B. A new operative technique of paratopic positioning of pediatric en bloc kidneys for transplantation. *Clin Transplant* 1994;8(2 Pt 1):139-43.
71. Kayler LK, Magliocca J, Kim RD *et al.* Single kidney transplantation from young pediatric donors in the United States. *Am J Transplant* 2009;9:2745-51.
72. Zhu L, Fu C, Chen S *et al.* Successful single-kidney transplantation in adult recipients using pediatric donors aged 8 to 36 months: comparable outcomes with those using pediatric donors aged > 3 years. *Transplantation* 2019;103:2388-96.
73. Suneja M, Kuppachi S, Katz D, Hunsicker L. Small pediatric kidneys expand the donor pool: an analysis of the scientific registry of transplant recipients (SRTR) data. *Transplantation* 2019;103:2549-57.
74. Booster MH, Wijnen RM, Vroemen AM *et al.* In situ preservation of kidneys from non-heart-beating donors – a proposal for a standardized protocol. *Transplantation* 1993;56(3):613-17.
75. Weber M, Dindo D, Demartines N *et al.* Kidney transplantation from donors without a heartbeat. *N Engl J Med* 2002;347(4):248-55.
76. del Rio F, Andrés A, Padilla M *et al.* Kidney transplantation from donors after uncontrolled circulatory death: the Spanish experience. *Kidney International* 2019;95:420-28.
77. Alonso A, Fernández-Rivera C, Villaverde P *et al.* Renal transplantation from non-heart-beating donors: a single-center 10-year experience. *Transplant Proc* 2005;37(9):3658-60.

78. Valero R, Cabrer C, Oppenheimer F *et al.* Normothermic recirculation reduces primary graft dysfunction of kidneys obtained from non-heart-beating donors. *Transpl Int* 2000;13(4):303-10.
79. Sánchez-Fructuoso AI, Prats D, Torrente J *et al.* Renal transplantation from non-heart-beating donors: a promising alternative to enlarge the donor pool. *J Am Soc Nephrol* 2000;11(2):350-8.
80. Andrés A, Gutiérrez E, Dipalma T *et al.* Successful kidney transplantation from helicopter transported deceased after cardiac death (DCD) donors with irreversible cardiac arrest in the street or at home far from the hospital [abstract 642]. *Am J Transplant* 2011; 11(Suppl 2):224.
81. Rao PS, Schaubel DE, Guidinger MK *et al.* A comprehensive risk quantification score for deceased donor kidneys: the Kidney Donor Risk Index. *Transplantation* 2009;88:231-6.
82. Pascual J, Pérez-Saéz MJ. Kidney Donor Profile Index: can it be extrapolated to our environment? *Nefrologia* 2016;36:465-8.
83. Lee A, Abramowicz D. Is the Kidney Donor Risk Index a step forward in the assessment of deceased donor kidney quality? *Nephrol Dial Transplant* 2015; 30(8):1285-90.
84. Friedewald JJ. Utilization and outcomes of marginal kidneys – using Kidney Donor Risk Index to move beyond the current labels. *Am J Transpl* 2012;12:1971-2.
85. Chan S, Campbell S, Clayton P *et al.* Temporal changes in deceased kidney donor characteristics in Australia. *Transplant Direct* 2016;2:e112.
86. Sypek M, Ullah S, Hughes P *et al.* Examining the increased rates of donor kidney nonutilization in Australia: what has changed? *Transplantation* 2019; 103:2582-90.
87. Dahmen M, Becker F, Pavenstädt H *et al.* Validation of the kidney donor profile index (KDPI) to assess a deceased donor's kidneys' outcome in a European cohort. *Scientific Reports* 2019;9:11234. https://doi.org/10.1038/s41598-019-47772-7.
88. Heilmann R, Green E, Reddy K *et al.* Potential impact of risk and loss aversion on the process of accepting kidneys for transplantation. *Transplantation* 2017;101: 1514-17.
89. Aria-Cabrales C, Pérez-Sáez MJ, Redondo-Pachón D *et al.* Usefulness of KDPI in Spain: a comparison with donor age and definition of standard/expanded criteria donor. *Nefrologia* 2018;38:503-13. https://doi.org/10.1016/j.nefro.2018.03.003.
90. Bui K, Kilambi V, Mehrotra S. Functional status-based risk-benefit analyses of high-KDPI kidney transplant versus dialysis. *Transpl Int* 2019;32:1297-1312.
91. Holscher C, Bowring M, Haugen C *et al.* National variation in increased infectious risk kidney offer acceptance. *Transplantation* 2019;131:2157-63.
92. Technical Working Group of Organ Procurement Committee of Eurotransplant: The ET-future of donor characterization: Step 1: Structured documentation of technical investigations for improved quality and safety. Annual Meeting of Eurotransplant Foundation, Leiden, Netherlands, 2015, available at https://my.eurotransplant.org/projects-themes/?target=cold (restricted access), accessed 16 May 2021.
93. Mensink J, Pol R, Nijboer W *et al.* Whole body CT Imaging in deceased donor screening for malignancies. *Transplantation Direct* 2019;5:e509. DOI:10.1097/TXD 0000000000000953.
94. Ploeg R, D'Alessandro A, Knechtle SJ *et al.* Risk factors for primary dysfunction after liver transplantation – a multivariate analysis. *Transplantation* 1993;55:807-13.
95. Yersiz H, Shaked A, Olthoff K *et al.* Correlation between donor age and the pattern of liver graft recovery after transplantation. *Transplantation* 1995;60:790-4.
96. Emre S, Schwartz ME, Altaca G *et al.* Safe use of hepatic allografts from donors older than 70 years. *Transplantation* 15 July 1996;62(1):62-5.
97. Jiménez Romero C, Moreno González E, Colina Ruíz F *et al.* Use of octogenarian livers safely expands the donor pool. *Transplantation* 1999;68:572-5.
98. Cuende N, Grande L, Sanjuán F *et al.* Liver transplant with organs from elderly donors: Spanish experience with more than 300 liver donors over 70 years of age. *Transplantation* 2002;73:1360.
99. Cescon M, Grazi GL, Ercolani G *et al.* Long-term survival of recipients of liver grafts from donors older than 80 years: is it achievable? *Liver Transp* 2003;9: 1174-80.
100. Nardo B, Masetti M, Urbani L *et al.* Liver transplantation from donors aged 80 years and over: pushing the limit. *Am J Transplant* 2004;4:1139-47.
101. Kim DY, Cauduro SP, Bohorquez HE *et al.* Routine use of livers from deceased donors older than 70: is it justified? *Transpl Int* 2005;18(1):73-7.
102. Cescon M, Grazi GL, Cucchetti A *et al.* Improving the outcome of liver transplantation with very old donors with updated selection and management criteria. *Liver Transpl* 2008;14(5):672-9.
103. Reese P, Sonawane S, Thomasson A *et al.* Donor age and cold ischemia interact to produce inferior 90-day liver allograft surival. *Transplantation* 2008;85(12): 1737-44.
104. Halldorson JB, Bakthavatsalam R, Fix O *et al.* D-Meld, a simple predictor of post liver transplant mortality for optimization of donor/recipient matching. *Am J Transpl* 2009;9(2):318-26.
105. Singhal A, Sezginsoy B, Ghuloom AE *et al.* Orthotopic liver transplant using allografts from geriatric

population in the United States: is there any age limit? *Exp Clin Transplant* 2010;8(3):196-201.

106. Faber W, Seehofer D, Puhl G *et al.* Donor age does not influence 12-month outcome after orthotopic liver transplantation. *Transplant Proc* 2011;43(10):3789-95.
107. Kim DY, Moon J, Island ER *et al.* Liver transplantation using elderly donors: a risk factor analysis. *Clin Transplant* 2011;25(2):270-6.
108. Lai Q, Melandro F, Levi Sandri GB *et al.* Use of elderly donors for liver transplantation: has the limit been reached? *J Gastrointestin Liver Dis* 2011;20(4):383-7.
109. Sampedro B, Cabezas J, Fábrega E *et al.* Liver transplantation with donors older than 75 years. *Transplant Proc* 2011;43(3):679-82.
110. Frühauf NR, Fischer-Fröhlich CL, Kutschmann M *et al.* Joint impact of donor and recipient parameters on the outcome of liver transplantation in Germany. *Transplantation* 2011;92(12):1378-84.
111. Akkina SK, Asrani SK, Peng Y *et al.* Development of organ-specific donor risk indices. *Liver Transpl* 2012; 18(4):395-404.
112. Feng S, Lai JC. Expanded criteria donors. *Clin Liver Dis* 2014;18(3):633-49.
113. Ghinolfi D, De Simone P, Lai Q *et al.* Risk analysis of ischemic-type biliary lesions after liver transplant using octogenarian donors. *Liver transplantation* 2016:22(5):588-98.
114. Ghinolfi D, Marti J, De Simone P *et al.* Use of octogenarian donors for liver transplantation: a survival analysis. *Am J Transpl* 2014;14(9);2062-71.
115. Jiménz-Romero C, Maesto OC, Molero FC *et al.* Using old liver grafts for liver transplantation: where are the limits? *World J Gastroenterol* 2014;20(31):10691-702.
116. Lai JC, Covinsky K, Feng S. The octogenarian donor: can the liver be "younger than stated age"? *Am J Transpl* 2014;14(9):1962-3.
117. Chedid M, Rossen C, Nyberg S, Heimbach J. Excellent long-term patient and graft survival are possible with appropriate use of livers from deceased septuagenarian and octogenarian donors. *HPB (Oxford)* 2014; 16(9):852-8.
118. Thorsen T, Aandahl EM, Bennet W *et al.* Transplantation with livers from deceased donors older than 75 years. *Transplantation* 2015;99(12):2534-42.
119. Bloom M, Raza S, Bhakta A *et al.* Impact of deceased organ donor deomgraphics and critical care end points on liver transplantation and graft survival rates. *J Am Coll Surg* 2015;220(1):38-47.
120. Lué A, Solanas E, Baptista P *et al.* How important is donor age in liver transplantation? *World J Gastroenterol* 2016;22(21);4966-76.
121. de Boer JD, Koopman JJ, Metselaar HJ *et al.* Liver transplantation with geriatric liver allografts: the current situation in Eurotransplant. *Transpl Int* 2017;30(4):432-3 [epub ahead, https://doi.org/10.111/tri.12914].
122. Pratschke J, Bender A, Boesch F *et al.* Association between donor age and risks of graft failure after liver transplantation: an analysis of the Eurotransplant database. *Transplant Int* 2019;32:270-79. DOI:10.1111/tri.13357.
123. Lozanovski V, Khajeh E, Fonouni H *et al.* The impact of major extended donor criteria on graft failure and patient mortality after liver transplantation. *Langenbecks Arch Surg* 2018;403:719-31. https://doi.org/10.1007/s00423-018-1704-z.
124. Haugen C, Bowring M, Holscher C *et al.* Survival benefit of accepting livers from deceased donors over 70 years old. *Am J Transplant* 2019;19:2020-28.
125. Caso-Maestro O, Jiménez-Romero C, Justo-Alonso I *et al.* Analyzing predictors of graft survival in patients undergoing liver transplantation with donors aged 70 years and over. *World J Gastroenterol* 2018;24: 5391-5402.
126. Cameron A, Busuttil RW. AASLD/ILTS transplant course: is there an extended donor suitable for everyone? *Liver Transpl* 2005 November:11(Suppl 2): S2-S5.
127. Rauchfuss F, Voigt R, Dittmar Y *et al.* Liver transplantation utilizing old donor organs: a German single-center experience. *Transplant Proc* 2010;42(1): 175-7.
128. Fouzas I, Sgourakis G, Nowak KM *et al.* Liver transplantation with grafts from septuagenarians. *Transplant Proc* 2008;40(9):3198-3200.
129. Saidi RF. Changing pattern of organ donation and utilization in the USA. *Int J Organ Transplant Med* 2012;3(4):149-56.
130. Loinaz C, González EM. Marginal donors in liver transplantation. *Hepato-gastroenterology* 2000;47(31): 256-63.
131. Sharkey FE, Lytvak I, Prihoda TJ *et al.* High-grade microsteatosis and delay in hepatic function after orthotopic liver transplantation. *Hum Pathol* 2011;42(9): 1337-42.
132. George J, Pera N, Phung N *et al.* Lipid peroxidation, stellate cell activation and hepatic fibrogenesis in a rat model of chronic steatohepatitis. *J Hepatol* 2003;39(5): 756-64.
133. Gabrielli M, Moisan F, Vidal M *et al.* Steatotic livers. Can we use them in OLTX? Outcome data from a prospective baseline liver biopsy study. *Ann Hepatol* 2012; 11(6):891-8.
134. Ghinolfi D, Rreka E, De Tata V *et al.* Pilot, open, randomized, prospective trial for normothermic machine perfusion evaluation in liver transplantation from older donors. *Liver Transpl* 2019;25(3):436-49.
135. Thuluvath PJ, Guidinger MK, Fung JJ *et al.* Liver

transplantation in the United States, 1999–2008. *Am J Transplant* 2010;10(4 Pt 2):1003-19.

136. Kim WR, Therneau TM, Benson JT *et al.* Deaths on the liver transplant waiting list: an analysis of competing risks. *Hepatology* 2006;43(2):345-51.
137. Peralta C, Jiménez-Castro MB, Gracia-Sancho J. Hepatic ischemia and reperfusion injury: effects on the liver sinusoidal milieu. *J Hepatol* 2013;59(5):1094-1106.
138. Van Golen RF, van Gulik TM, Heger M. The sterile immune response during hepatic ischemia/reperfusion. *Cytokine Growth Factor Rev* 2012;23(3):69-84.
139. Cywinski JB, Mascha E, Miller C *et al.* Association between donor–recipient serum sodium differences and orthotopic liver transplant graft function. *Liver Transpl* 2008;14(1):59-85.
140. Doyle M, Vachharajani N, Wellen J *et al.* Short- and long-term outcome after steatotic liver transplantation. *Arch Surg* 2010;145(7):653-60.
141. Pezzati D, Ghinolfi D, De Simone P *et al.* Strategies to optimize the use of marginal donors in liver transplantation. *World J Hepatol* 2015;7(26):2636-47.
142. Adam R, Sanchez C, Astarcioglu I *et al.* Deleterious effect of extended cold ischemia time on the post-transplant outcome of aged livers. *Transplant Proc* 1995;27(1):1181-3.
143. Feng S, Goodrich NP, Bragg-Gresham JL *et al.* Characteristics associated with liver graft failure: the concept of a donor risk index. *Am J Transplant* 2006; 6(4):783-90.
144. Yersiz H, Renz JF, Farmer DG *et al.* One hundred *in situ* split-liver transplantations: a single-center experience. *Ann Surg* 2003;238(4):496-505.
145. Mojtabee M, Ghorbani F, Nikeghbalian S *et al.* Liver procurement from poisoned donors: a survival study. *Experimental and Clinical Transplantation* 2020;18: 334-8. DOI:10.6002/ect2018.0339.
146. Braat AE, Blok JJ, Putter H *et al.* European Liver and Intestine Transplant Association (ELITA) and Eurotransplant Liver Intestine Advisory Committee (ELIAC). The Eurotransplant donor risk index in liver transplantation: ET-DRI. *Am J Transplant* 2012 Oct; 12(10):2789-96.
147. Blok JJ, Braat AE, Adam R *et al.* Validation of the donor risk index in orthotopic liver transplantation within the Eurotransplant region. *Liver Transpl* 2012; 18(1):112-19.
148. Mangus RS, Fridell JA, Kubal CA *et al.* Elevated alanine aminotransferase (ALT) in the deceased donor: impact on early post-transplant liver allograft function. *Liver Int* 2015;35(2):524-31.
149. Radunz S, Paul A, Nowak K *et al.* Liver transplantation using donor organs with markedly elevated liver enzymes: how far can we go? *Liver Int* 2011;31:1021-7.
150. Powner DJ. Factors during donor care that may affect liver transplantation outcome. *Prog Transplant* 2004; 14(3):241-7; quiz 248-9.
151. D'Alessandro A, Kalayoglu M, Sollinguer H *et al.* The predictive value of donor liver biopsies for the development of primary nonfunction after orthotopic liver transplantation. *Transplantation* 1991;51:157-63.
152. Urena MA, Moreno Gonzalez E, Romero CJ *et al.* An approach to the rational use of steatotic donor livers in liver transplantation. *Hepato-gastroenterology* 1999;46(26):1164-73.
153. Rey JW, Wirges U, Dienes HP *et al.* Hepatic steatosis in organ donors: disparity between surgery and histology? *Transplant Proc* 2009;41(6):2557-60.
154. Fischer-Fröhlich CL, Frühauf NR, Schleicher C *et al.* Analysis of competing failure risks reveals proper liver assessment at recovery excluding severe steatosis as crucial compared to other cumulative extended donor criteria. *Organs, Tissues and Cells* 2012;15:115-22.
155. de Graaf EL, Kench J, Dilworth P *et al.* Grade of deceased donor liver macrovesicular steatosis impacts graft and recipient outcomes more than the donor risk index. *J Gastroenterol Hepatol* 2012;27(3):540-6.
156. Flechtenmacher C, Schirmacher P, Schemmer P. Donor liver histology – a valuable tool in graft selection. *Langenbecks Arch Surg* 2015;400(5):551-7.
157. Heller B, Peters S. Assessment of liver transplant donor biopsies for steatosis using frozen section: accuracy and possible impact on transplantation. *J Clin Med Res*. 2011;3(4):191-4.
158. Avolio AW, Frongillo F, Nicolotti N *et al.* Successful use of extended criteria donor grafts with low to moderate steatosis in patients with model for end-stage liver disease scores below 27. *Transplant Proc* 2009 Jan-Feb;41(1):208-12.
159. Briceño J, Ciria R, Pleguezuelo M *et al.* Impact of donor graft steatosis on overall outcome and viral recurrence after liver transplantation for hepatitis C virus cirrhosis. *Liver Transpl* 2009;15(1):37-48.
160. Cucchetti A, Vivarelli M, Ravaioli M *et al.* Assessment of donor steatosis in liver transplantation: is it possible without liver biopsy? *Clin Transplant* 2009; 23(4):519-24.
161. Noujaim HM, de Ville de Goyet J, Montero EF *et al.* Expanding *post mortem* donor pool using steatotic liver grafts: a new look. *Transplantation* 2009;87(6): 919-25.
162. Verran D, Kusyk T, Painter D *et al.* Clinical experience gained from the use of 120 steatotic donor livers for orthotopic liver transplantation. *Liver Transpl* 2003;9(5):500-5.
163. Yeriz H, Lee C, Kaldas F *et al.* Assessment of hepatic steatosis by transplant surgeon and expert pathologist: a prospective double blind evaluation of 201 donor livers. *Liver Transpl* 2013;19(4):437-49.
164. Yerian L. Liver donor organ evaluation. Chapter 3.1 In:

Cagle PT, Yerian L, Truong L, eds: *Atlas of Transplant Pathology*. Northfield IL: College of American Pathologists Press, 2015, ISBN 9781941096239.

165. Transplant Pathology Internet Services, Transplant Pathology at the University of Pittsburgh, PA. Liver: Biopsy evaluation of the donor organ: frozen sections, available at https://tpis.upmc.com/changebody.cfm?url=/tpis/liver/LDonorFS.jsp, accessed 15 May 2021.
166. Spitzer AL, Oliver Lao OB, Dick AA *et al.* The biopsied donor liver: incorporating macrosteatosis into high-risk donor assessment. *Liver Transpl* 2010;16(7):874-84.
167. Croome K, Lee D, Croome S *et al.* The impact of postreperfusion syndrome during liver transplantation using livers with significant macrosteatosis. *Am J Transplant* 2019;19:1-10 [epub ahead] https://doi.org/10.1111/ajt.15330.
168. Liu Z, Jia J, Ning H *et al.* Systematic evaluation of the safety threshold for allograft macrovesicular steatosis in cadaveric liver transplantation. *Frontiers in Physiology* 2019;10;Article 429. https://doi.org/10.3389/fphys.2019.00429.
169. Zhang, OY, Zhang OF, Zhang DZ. The impact of steatosis on the outcome in liver transplantation: a meta-analysis. *BioMed Research International* 2019; Article ID 3962785. https://doi.org/10.1155/2019/3962785.
170. Oliver J, Machineni P, Bongu A *et al.* Liver biopsy in assessment of extended criteria donors. *Liver Transpl* 2018;24:182-91.
171. Beltzer C, Quante M, Rheinsberger M *et al.* Perkutante Leberbiopsie vor Organentnahme – Einfluss auf die Organallokation und Kosten in der Lebertransplantation ['Percutaneous liver biopsy before organ removal – impact on organ allocation and costs in liver transplantation'; in German]. *Chirurg* 2020;251:[epub ahead]. https://doi.org/10.1007/s00104-020-01192-w.
172. Lauterio A, Di Sandro S, Concone G *et al.* Current status and perspectives in split liver transplantation. *World J Gastroenterol* 2015 Oct 21;21(39):11003-15.
173. Becker J, Czigany, Bednarsch J *et al.* Potential value and limitations of different clinical scoring systems in the assessment of short- and long-term outcome following orthotopic liver transplantation. *PLoS ONE* 2019;14:e0214221. https://doi.org/10.1371/journal.pone.0214221.
174. Winter A, Féray C, Audureaun E *et al.* External validation of the donor risk index and the Eurotransplant donor risk index on the French liver transplantation registry. *Liver Int* 2017 [e-pub ahead: February 2017, 10.1111/liv.13378:1-10].
175. Blok JJ, Putter H, Rogiers X *et al.* Combined effect of donor and recipient risk on outcome after liver transplantation: research of the Eurotransplant database. *Liver Transpl* 2015;21:1486-93.
176. Foley DP, Fernández LA, Leverson G *et al.* Biliary complications after liver transplantation from donation after cardiac death donors: an analysis of risk factors and long-term outcomes from a single center. *Ann Surg* 2011;253(4):817-25.
177. Taner CB, Bulatao IG, Perry DK *et al.* Asystole to cross-clamp period predicts development of biliary complications in liver transplantation using donation after cardiac death donors. *Transpl Int* 2012;25(8):838-46.
178. Taner CB, Bulatao IG, Willingham DL *et al.* Events in procurement as risk factors for ischemic cholangiopathy in liver transplantation using donation after cardiac death donors. *Liver Transpl* 2012;18(1):100-11.
179. Abt P, Crawford M, Desai N *et al.* Liver transplantation from controlled non-heart-beating donors: an increased incidence of biliary complications. *Transplantation* 2003;75(10):1659-63.
180. Fondevila C, Hessheimer AJ, Flores E *et al.* Applicability and results of Maastricht type 2 donation after cardiac death liver transplantation. *Am J Transplant* 2012;12(1):162-70.
181. Blok JJ, Detry O, Putter H *et al.* Longterm results of liver transplantation from donation after circulatory death. *Liver Transpl* 2016;22(8):1107-14.
182. Eurotransplant Foundation: *Eurotransplant manual*, Chapter 7: ET-Pancreas allocation system (EPAS). Leiden, Netherlands: Eurotransplant Foundation, 2013, available at www.eurotransplant.org/patients/eurotransplant-manual/, accessed 15 May 2021.
183. Neidlinger NA, Odorico JS, Sollinger HW *et al.* Can 'extreme' pancreas donors expand the donor pool? *Curr Opin Organ Transplant* 2008;13(1):67-71.
184. Singh RP, Rogers J, Farney AC *et al.* Outcomes of extended donors in pancreatic transplantation with portal-enteric drainage. *Transplant Proc* 2008;40(2):502-5.
185. Axelrod DA, Sung RS, Meyer KH *et al.* Systematic evaluation of pancreas allograft quality, outcomes and geographic variation in utilization. *Am J Transplant* 2010;10(4):837-45.
186. Stegall MD, Dean PG, Sung R *et al.* The rationale for the new deceased donor pancreas allocation schema. *Transplantation* 2007;83(9):1156-61.
187. Salvalaggio PR, Schnitzler MA, Abbott KC *et al.* Patient and graft survival implications of simultaneous pancreas kidney transplantation from old donors. *Am J Transplant* 2007;7(9):1561-71.
188. Gruessner RW, Sutherland DE, Gruessner AC. Mortality assessment for pancreas transplants. *Am J Transplant* 2004;4(12):2018-26.
189. Fernandez LA, Di Carlo A, Odorico JS *et al.*

Simultaneous pancreas-kidney transplantation from donation after cardiac death: successful long-term outcomes. *Ann Surg* 2005;242(5):716-23.

190. Andreoni KA, Brayman KL, Guidinger MK *et al.* Kidney and pancreas transplantation in the United States, 1996–2005. *Am J Transplant* 2007;7(5 Pt 2): 1359-75.
191. Muthusamy AS, Vaidya AC, Sinha S *et al.* Alemtuzumab induction and steroid-free maintenance immunosuppression in pancreas transplantation. *Am J Transplant* 2008;8(10):2126-31.
192. Berney T, Kandaswamy R. Invited commentary: who needs a pancreas donor risk index? *Transpl Int* 2015; 28(9):1025-7.
193. Matsumoto I, Sawada T, Nakano M *et al.* Improvement in islet yield from obese donors for human islet transplants. *Transplantation* 2004 Sep 27;78(6):880-5.
194. Maglione M, Ploeg RJ, Friend PJ. Review: Donor risk factors, retrieval technique, preservation and ischemia/reperfusion injury in pancreas transplantation. *Curr Opin Organ Transplant* 2013;18(1):83-8.
195. Blok JJ, Kopp WH, Verhagen MJ *et al.* The value of PDRI and P-PASS as predictors of outcome after pancreas transplantation in a large European pancreas transplantation center. *Pancreas* 2016;45(3):331-6.
196. Mittal S, Lee F, Bradbury L *et al.* Validation of the pancreas donor risk index for use in a UK population. *Transpl Int* 2015;28(9):1028-33.
197. Nadalin S, Capobianco I, Hulik S. Pancreas procurement. Chapter 15: In: Aseni P, Grande AM, De Carlis L, eds. *Multiorgan procurement for transplantation*. Berlin: Springer Verlag, 2016, 1st edn:165-82. ISBN 978-3-319-28414-9.
198. Loss M, Drewitz KP, Apfelbacher CJ *et al.* Why offered pancreases are refused in the allocation process – a descriptive study using routine data from Eurotransplant. *Transplantation* 2013;95(9):1134-41.
199. Marang-van de Mheen PJ, Hilling DE, Dirkes MC, Baranski AG. Surgical injuries of pancreatic allografts during procurement. *Clin Transplant* 2011;25(5):737-43.
200. de Boer JD, Kopp WH, Ooms K *et al.* Abdominal organ procurement in the Netherlands – an analysis of quality and clinical impact. *Transpl Int* 2017;30: 288-94.
201. Lam HD, Schaapherder AF, Kopp WH *et al.* Professionalization of surgical abdominal organ recovery leading to an increase in pancreatic allografts accepted for transplantation in the Netherlands: a serial analysis. *Transpl Int* 2017;30(2):117-23.
202. Kopp WH, de Vries E, de Boer J *et al.* Donor risk indices in pancreas allocation in the Eurotransplant region. *Transpl Int*. 2016;29:921-9.
203. Shahrestani S, Webster AC, Lam VW *et al.* Outcomes from pancreatic transplantation in donation after cardiac death: a systematic review and meta-analysis. *Transplantation* 2017;101(1):122-30.
204. Spaggiari M, Bissing M, Campara M *et al*, Pancreas transplantation from pediatric donors: a United Network of Organ Sharing registry analysis. *Transplantation* 2017;101:2484-91.
205. Nordström J, Lundgren M, Jorns C *et al.* First European case of simultaneous liver and pancreas transplantation as treatment for Wolcott-Rallison syndrome in a small child. *Transplantation* 2020; 104(3):522-5.
206. Langnas A, Goulet O, Quigley E, Tappenden K, eds. *Intestinal Failure: Diagnosis, Management and Transplantation*. Malden MA: Blackwell, 2008, ISBN 978-1-4051-4637-1.
207. Vianna RM, Mangus RS, Tector AJ. Current status of small bowel and multivisceral transplantation. *Adv Surg* 2008;42:129-50.
208. Rushton SN, Hudson AJ, Collett D *et al.* Strategies for expanding the UK pool of potential intestinal transplant donors. *Transplantation* 2013;95(1):234-9.
209. Matsumoto CS, Kaufman SS, Girlanda R *et al.* Utilization of donors who have suffered cardiopulmonary arrest and resuscitation in intestinal transplantation. *Transplantation* 2008;86(7):941-6.
210. Forni A, Luciani GB, Chiominto B *et al.* Results with expanded donor acceptance criteria in heart transplantation. *Transplant Proc* 2011;43(4):953-9.
211. Forni A, Luciani GB, Chiominto B *et al.* Impact of donor quality on outcome of heart transplantation. *Eur J Cardiothorac Surg* 2010;38(6):788-94.
212. Schüler S, Matschke K, Loebe M *et al.* Coronary artery disease in patients with hearts from older donors: morphologic features and therapeutic implications. *J Heart Lung Transplant* 1993;12(1 Pt 1):100-109.
213. Luciani G, Livi U, Faggian G *et al.* Clinical results of heart transplantation in recipients over 55 years of age with donors over 40 years of age. *J Heart Lung Transplant* 1992;11(6):1177-83.
214. Potapov EV, Loebe M, Hübler M *et al.* Medium-term results of heart transplantation using donors over 63 years of age. *Transplantation* 1999;68(12):1834-8.
215. Lietz K, John R, Mancini DM *et al.* Outcomes in cardiac transplant recipients using allografts from older donors versus mortality on the transplant waiting list; implications for donor selection criteria. *J Am Coll Cardiol* 2004;43(9):1553-61.
216. Bruschi G, Colombo T, Oliva F *et al.* Orthotopic heart transplantation with donors greater than or equal to 60 years of age: a single-center experience. *Eur J Cardiothorac Surg* 2011;40(1):e55-e61.
217. Mancini DM, Schulze PC, Jiang J *et al.* Cardiac transplantation in over 2000 patients: a single-institution

experience from Columbia University. *Clin Transpl* 2011;25:157-75.

218. Zeissig SR, Fischer-Froehlich CL, Polster F *et al.* Current practice of heart donor evaluation in Germany: multivariable risk factor analysis confirms practicability of guidelines. *J Transplant* 2013:Article 701854. https://doi.org/10.1155/2013/701854.
219. Kutschmann M, Fischer-Fröhlich CL, Schmidtmann I *et al.* The joint impact of donor and recipient parameters on the outcome of heart transplantation in Germany after graft allocation. *Transpl Int* 2014;27(2): 152-61.
220. Fischer-Fröhlich CL, Kutschmann M, Schmidtmann I *et al.* Outcome of heart transplantation in Germany: details to be considered beyond multivariate analysis to improve the quality of graft allocation. *Organs, Tissues and Cells* 2014;17:53-61.
221. Dorenta R, Gandjbakhchb E, Goéminnec C *et al.* Assessment of potential heart donors: A statement from the French heart transplant community ['Évaluation cardiaque des donneurs potentiels d'organes: mise au point des transplanteurs cardiaques français']. *Archives of Cardiovascular Disease* 2018;111:126-39.
222. Khush KK. Donor selection in the modern era. *Ann Cardiothorac Surg* 2018;7(1):126-34. DOI:10.21037/acs.2017.09.09.
223. Kilic A, Emani S, Sai-Sudhakar CB *et al.* Donor selection in heart transplantation. *J Thorac Dis* 2014;6:1097-1104. https://doi.org/10.3978/j.issn.2072-1439.2014.03.23.
224. Aliabadi-Zuckermann A, Gökler J, Kaider A *et al.* Donor heart selection and outcomes: an analysis of over 2000 cases. *J Heart Lung Transplant* 2018;37: 976-84.
225. Simion D, Casartelli ML, Procaccio F. Early targeted treatment may facilitate complete weaning from vasopressors and recovery of stunned hearts in unstable potential donors: a new golden time for organ retrieval? *Organs, Tissues and Cells* 2014;17:49-52.
226. Bombardini T, Gherardi S, Arpesella G *et al.* Favorable short-term outcome of transplanted hearts selected from marginal donors by pharmacological stress echocardiography. *J Am Soc Echocardiogr* 2011; 24(4):353-62.
227. Audibert G, Charpentier C, Seguin-Devaux C *et al.* Improvement of donor myocardial function after treatment of autonomic storm during brain death. *Transplantation* 2006;82(8):1031-6.
228. Borbely XI, Krishnamoorthy V, Modi S *et al.* Temporal changes in left ventricular systolic function and use of echocardiography in adult heart donors. *Neurocrit Care* 2015;23(1):66-71.
229. Santise G, D'Ancona G, Falletta C *et al.* Donor pharmacological hemodynamic support is associated with primary graft failure in human heart transplantation. *Interact Cardiovasc Thorac Surg* 2009;9(3):476-9.
230. Chamorro C, Romera MA, Silva JA *et al.* Can heart donation exclusion factors be overcome? *Rev Esp Cardiol* 2006;59(3):232-7 [in Spanish].
231. Shemie SD, Ross H, Pagliarello J *et al.* Organ donor management in Canada: recommendations of the forum on medical management to optimize donor organ potential. *CMAJ* 2006;174(6):S13-S32.
232. Kirk R, Dippchard A, Davies R *et al.* ISHLT consensus statement on donor organ acceptability and management in pediatric heart transplantation. *J Heart Lung Transplant* 2020;39:331-41.
233. Wood KE, Becker BN, McCartney JG *et al.* Current concepts: care of the potential organ donor. *N Engl J Med* 2004;351(26):2730-9.
234. Ryan JB, Hicks M, Cropper JR *et al.* Functional evidence of reversible ischemic injury immediately after the sympathetic storm associated with experimental brain death. *J Heart Lung Transplant* 2003;22(8):922-8.
235. Rosendale JD, Kauffman HM, McBride MA *et al.* Hormonal resuscitation yields more transplanted hearts, with improved early function. *Transplantation* 2003; 75(8):1336-41.
236. Novitzky D, Cooper DK, Rosendale JD *et al.* Hormonal therapy of the brain-dead organ donor: experimental and clinical studies. *Transplantation* 2006;82(11):1396-1401.
237. Costanzo MR, Dipchand A, Starling R *et al.* The International Society of Heart and Lung Transplantation (ISHLT) guidelines for the care of heart transplant recipients. *J Heart Lung Transplant* 2010;29(8):914-56.
238. Wittwer T, Wahlers T. Marginal donor grafts in heart transplantation: lessons learned from 25 years of experience. *Transpl Int* 2008;21(2):113-25.
239. Fischer-Fröhlich CL, Lauchart W. Evaluation of heart function in organ donors. *Organs Tissues and Cells* 2008;11:101-17.
240. Oras J, Doueh R, Norberg E *et al.* Left ventricular dysfunction in potential donors and its influence on recipients outcomes. *J Thorac Cardiovasc Surg* 2020; 159: 1333-1341 https://doi.org/10.1016/j.jtcvs.2019.06.070.
241. Grauhan O, Siniawski H, Dandel M *et al.* Coronary atherosclerosis of the donor heart – impact on early graft failure. *Eur J Cardiothorac Surg* 2007;32(4):634-8.
242. Grauhan O, Wesslau C, Hetzer R. Routine screening of donor hearts by coronary angiography is feasible. *Transplant Proc* 2006;38(3):666-7.
243. Grosu A, Bombardini T, Senni M *et al.* End-systolic pressure/volume relationship during dobutamine stress echo: a prognostically useful non-invasive index of left ventricular contractility. *Eur Heart J* 2005;26:2404-12.
244. Van Raemdonck D, Rega F, Rex S *et al.* Machine

perfusion of thoracic organs. *J Thorac Dis* 2018 Apr; 10(Suppl 8):S910-S923. https://doi.org/10.21037/jtd.2018.02.85.

245. Tsui SSL, Oniscu GC. Extending normothermic regional perfusion to the thorax in donors after circulatory death. *Curr Opin Organ Transplant* 2017 Jun;22(3):245-50. https://doi.org/10.1097/MOT.0000000000000413.
246. Patel ND, Weiss ES, Nwakanma LU *et al.* Impact of donor-to-recipient weight ratio on survival after heart transplantation. Analysis of the United Network for Organ Sharing database. *Circulation* 2008; 118(Suppl 1):S83-S88. *Circulation* is available at www.ahajournals.org/journals/circ. https://doi.org/10.1161/CIRCULATIONAHA.107.756866.
247. Lowalekar SK, Cao H, Lu XG *et al.* Subnormothermic preservation in somah: a novel approach for enhanced functional resuscitation of donor hearts for transplant. *Am J Transplant* 2014;14(10):2253-62.
248. Zaroff JG, Babcock WD, Shiboski SC *et al.* Temporal changes in left ventricular systolic function in heart donors: results of serial echocardiography. *J Heart Lung Transplant* 2003;22(4):383-8.
249. Smith SC Jr, Feldman TE, Hirshfeld JW Jr *et al.* Guidelines for percutaneous transluminal coronary angioplasty. A report of the ACC/AHA Task Force on Assessment of Diagnostic and Therapeutic Cardiovascular Procedures (Subcommittee on percutaneous transluminal coronary angioplasty). *Circulation* 1988; 78:486-502.
250. Warnecke G, Moradiellos J, Tudorache I *et al.* Normothermic perfusion of donor lungs for preservation and assessment with the Organ Care System Lung before bilateral transplantation: a pilot study of 12 patients. *Lancet* 2012;380(9856):1851-8.
251. de Perrot M, Liu M, Waddell TK *et al.* Ischemia-reperfusion induced lung injury. *Am J Respir Crit Care Med* 2003;167(4):490-511.
252. Christie JD, Van Raemdonck D, de Perrot M *et al* Report of the ISHLT Working Group on primary lung graft dysfunction, Part I: introduction and methods. *J Heart Lung Transplant* 2005;24(10):1451-3.
253. Bhorade S, Vigneswaran W, McCabe M *et al.* Liberalization of donor criteria may expand the donor pool without adverse consequence in lung transplantation. *J Heart Lung Transplant* 2000;19(12):1199-1204.
254. Belhaj A, Dewachter L, Rorive S *et al.* Mechanical versus humoral determinants of brain death-induced lung injury. *PLoS One* 2017; 12(2): e0181899. https://doi.org/10.1371/journal.pone.0181899.
255. De Soyza AG, Dark JH, Parums DV *et al.* Donor acquired small cell lung cancer following pulmonary transplantation. *Chest* 2001;120:1030-1.
256. de Perrot M, Wigle DA, Pierre AF *et al.* Bronchogenic carcinoma after solid organ transplantation. *Ann Thorac Surg* 2003;75(2):367-71.
257. Diamond JM, Lee JC, Kawut SM *et al.* Clinical risk factors for primary graft dysfunction after lung transplantation. *Am J Respir Crit Care Med* 2013;187(5): 527-34.
258. Bonser RS, Taylor R, Collett D *et al.* Cardiothoracic Advisory Group to NHS Blood and Transplant and the Association of Lung Transplant Physicians (UK). Effect of donor smoking on survival after lung transplantation: a cohort study of a prospective registry. *Lancet* 2012;380(9843):747-55.
259. Taghavi S, Jayarajan S, Komaroff E *et al.* Double-lung transplantation can be safely performed using donors with heavy smoking history. *Ann Thorac Surg* 2013; 95(6):1912-17.
260. Berman M, Goldsmith K, Jenkins D *et al.* Comparison of outcomes from smoking and nonsmoking donors: thirteen-year experience. *Ann Thorac Surg* 2010;90(6): 1786-92.
261. Oto T, Griffiths AP, Levvey B *et al.* A donor history of smoking affects early but not late outcome in lung transplantation. *Transplantation* 2004;78(4):599-606.
262. Mattner F, Kola A, Fischer S *et al.* Impact of bacterial and fungal donor organ contamination in lung, heart-lung, heart and liver transplantation. *Infection* 2008; 36(3):207-12.
263. Campos S, Caramori M, Teixeira R *et al.* Bacterial and fungal pneumonias after lung transplantation. *Transplant Proc* 2008;40(3):822-4.
264. Bonde PN, Patel ND, Borja MC *et al.* Impact of donor lung organisms on post-lung transplant pneumonia. *J Heart Lung Transplant* 2006;25(1):99-105.
265. Weill D, Dey GC, Young KR *et al.* A positive donor Gram stain does not predict the development of pneumonia, oxygenation, or duration of mechanical ventilation following lung transplantation [abstract]. *J Heart Lung Transplant* 2001;20(2):255.
266. Zenati M, Dowling RD, Dummer JS *et al.* Influence of the donor lung on development of early infections in lung transplant recipients. *J Heart Lung Transplant* 1990;9(5):502-9.
267. Avlonitis VS, Krause A, Luzzi L *et al.* Bacterial colonization of the donor lower airways is a predictor of poor outcome in lung transplantation. *Eur J Cardiothorac Surg* 2003;24(4):601-7.
268. Zafar F, Khan MS, Heinle JS *et al.* Does donor arterial partial pressure of oxygen affect outcomes after lung transplantation? A review of more than 12,000 lung transplants. *J Thorac Cardiovasc Surg* 2012;143(4): 919-25.
269. Ruiz I, Gavaldá J, Monforte V *et al.* Donor-to-host transmission of bacterial and fungal infections in lung transplantation. *Am J Transplant* 2006;6(1):178-82.

270. Ciulli F, Tamm M, Dennis CM *et al.* Donor-transmitted bacterial infection in heart–lung transplantation. *Transplant Proc* 1993;25(1 Pt 2):1155-6.
271. Miñambres E, Pérez-Villares JM, Chico-Fernández M *et al.* Lung donor treatment protocol in brain dead-donors: a multicenter study. *J Heart Lung Transplant* 2015;34(6):773-80.
272. Angel LF, Levine DJ, Restrepo MI *et al.* Impact of a lung transplantation donor-management protocol on lung donation and recipient outcomes. *Am J Respir Crit Care Med* 2006;174(6):710-16.
273. Gauthier JM, Bierhals AJ, Liu J *et al.* Chest computed tomography imaging improves potential lung donor assessment. *J Thorac Cardiovasc Surg* 2019;157:1711-18.
274. McCowin MJ, Hall TS, Babcock WD *et al.* Changes in radiographic abnormalities in organ donors: associations with lung transplantation. *J Heart Lung Transplant* 2005;24(3):323-30.
275. Straznicka M, Follette DM, Eisner MD *et al.* Aggressive management of lung donors classified as unacceptable: excellent recipient survival one year after transplantation. *J Thorac Cardiovasc Surg* 2002; 124(2):250-8.
276. Verleden GM, Martens A, Ordies S *et al.* Radiological analysis of unused donor lungs: a tool to improve donor acceptance for transplantation? *Am J Transplant* 2017;17(7):1912-21. https://doi.org/10.1111/ajt.14255.
277. Puskas JD, Winton TL, Miller DJ *et al.* Unilateral donor lung dysfunction does not preclude successful contralateral single-lung transplantation. *J Thorac Cardiovasc Surg* 1992;103(5):1015-17.
278. Bolton JS, Padia SA, Borja MC *et al.* The predictive value and inter-observer variability of donor chest radiograph interpretation in lung transplantation. *Eur J Cardiothorac Surg* 2003;23(4):484-7.
279. Ghorbani F, Najafizadeh K, Fischer-Fröhlich CL, Mojtabae M. Impact of recruitment maneuvers to cover adverse effects of donor transfer. *Exp Clin Transplant* 2020;18:429-35. DOI:10.6002/ect.2019.236.
280. Núñez JR, Varela A, del Rio F *et al.* Bipulmonary transplants with lungs obtained from two non-heart-beating donors who died out of hospital. *J Thorac Cardiovasc Surg* 2004;127(1):297-9.
281. Gómez-de-Antonio D, Campo-Cañaveral JL, Crowley S *et al.* Clinical lung transplantation from uncontrolled non-heart-beating donors revisited. *J Heart Lung Transplant* 2012;31(4):349-53.
282. Suberviola B, Mons R, Ballesteros MA *et al.* Excellent long-term outcome with lungs obtained from uncontrolled donation after circulatory death. *Am J Transplant* 2019 Apr;19(4):1195-1201.
283. Warnecke G, Van Raemdonck D, Smith MA *et al.* Normothermic ex-vivo preservation with the portable Organ Care System Lung device for bilateral lung transplantation (INSPIRE): a randomised, open-label, non-inferiority, phase 3 study. *Lancet Respir Med* 2018 May;6(5):357-67. https://doi.org/10.1016/S2213-2600(18) 30136-X.
284. Loor G, Warnecke G, Villavicencio MA *et al.* Portable normothermic ex-vivo lung perfusion, ventilation, and functional assessment with the Organ Care System on donor lung use for transplantation from extended-criteria donors (EXPAND): a single-arm, pivotal trial. *Lancet Respir Med* 2019 Nov;7(11):975-84. https://doi.org/10.1016/S2213-2600(19) 30200-0.
285. Neyrinck A, Rega F, Jannis N *et al.* Ex vivo reperfusion of human lungs declined for transplantation: a novel approach to alleviate donor organ shortage? [abstract] *J Heart Lung Transplant* 2004;23(2 Suppl): S172-S173.
286. Wierup P, Haraldsson A, Nilsson F *et al.* Ex vivo evaluation of nonacceptable donor lungs. *Ann Thorac Surg* 2006;81(2):460-6.
287. Cypel M, Yeung JC, Liu M *et al.* Normothermic *ex vivo* lung perfusion in clinical lung transplantation. *N Engl J Med* 2011;364(15):1431-40.
288. Wallinder A, Ricksten SE, Hansson C *et al.* Transplantation of initially rejected donor lungs after *ex vivo* lung perfusion. *J Thorac Cardiovasc Surg* 2012; 144(5):1222-8.
289. Zych B, Popov AF, Stavri G *et al.* Early outcomes of bilateral sequential single lung transplantation after ex-vivo lung evaluation and reconditioning. *J Heart Lung Transplant* 2012;31(3):274-81.
290. Aigner C, Slama A, Hötzenecker K *et al.* Clinical *ex vivo* lung perfusion – pushing the limits. *Am J Transplant* 2012;12(7):1839-47.
291. Tait B, Süsal C, Gebel H *et al.* Consensus guidelines on the testing and clinical management issues associated with HLA and non-HLA antibodies in transplantation. *Transplantation* 2013;85:19-47.
292. Nickholgh A, Nikda M, Shafei S *et al.* Ex situ liver machine perfusion as an emerging graft protective strategy in clinical liver transplantation: the dawn of a new era. *Transplantation* 2019;103:2003-11.
293. Eshmuminov D, Becker D, Borrego LB *et al.* An integrated perfusion machine preserves injured human livers for 1 week. *Nat Biotechnol* 2020;38:189-98. https://doi.org/10.1038/s41587-019-0374-x.

Related material

Appendix 14. Donor examination by various means
Appendix 15. Grading for biopsies at histopathological examinations (English-language version)

Chapter 8. Risk of transmission of infectious diseases

8.1. Introduction

Acute or latent donor infections may be transmitted to recipients via the graft and may result in significant morbidity or mortality [1-3]. In the absence of suitable treatment for the recipient, organs should not be transplanted from a donor if there is strong evidence or strong suspicion of an infection in the donor. A decision to transplant organs from donors with certain infections – e.g. *Cytomegalovirus* (CMV), hepatitis B virus (HBV), hepatitis C virus (HCV) or human immunodeficiency virus (HIV) – may be taken for selected recipients, with an acceptable risk that is mitigated by monitoring and prophylactic or pre-emptive interventions [1, 4-5].

In the context of deceased donation, despite collection of detailed clinical and epidemiological information, there is not sufficient time for exhaustive diagnostic investigations, except for tests for which results are likely to be available within a few hours [5-6]. In donation procedures without such time constraints (e.g. live organ or deceased tissue donation), more extensive diagnostic procedures should be performed to reduce possible risks as part of a more comprehensive donor characterisation.

To assure the microbial safety of transplantation, besides national guidelines, locally applicable current and updated epidemiology of infectious diseases should be taken into account [7-8]. Recent experience with emerging local, geographically restricted or pandemic infections highlights the continually changing nature of the risk of infection transmission through transplantation. This risk is best addressed by *ad hoc* action plans on a national or international level – e.g. in the case of chikungunya virus, West Nile virus (WNV), Zika virus, Yellow fever virus, Ebola virus, Leishmania, hepatitis E virus (HEV), Borna virus, pandemic influenza H1N1 virus or the recent SARS-CoV-2 (Covid-19) pandemic [9-16].

Donor-derived infectious agents transmissible through organs or tissues can be divided into five groups of pathogens:

- Viruses: graft infection, with or without detectable viraemia.
- Bacteria: graft colonisation/infection, with or without bacteraemia.
- Fungi: graft colonisation/infection, with or without fungaemia.
- Parasites: acute or latent infection or acute infection, with or without parasitaemia.
- Prions: by infection.

The timeline for acquisition of infection in relation to the point of donation can be categorised as follows:

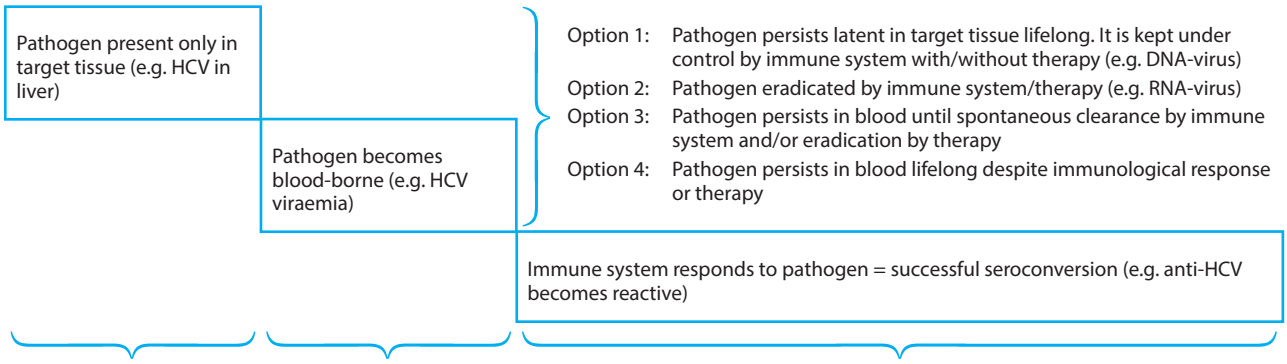
a. *Infection acquired in the past (e.g. CMV, Epstein–Barr virus, Strongyloides* spp.*).*
Screening is usually done by testing serum for the presence of antigens or antibodies to the pathogen. Antibody screening cannot differentiate whether a donor has cleared an infection or if a latent infection prevails in tissues or organs; when reactive, such screening indicates only previous exposure to the given pathogen. Latent infections in the donor can be

transmitted by a graft and may be reactivated in immunosuppressed recipients. If recipients are without previous immunological protection against the pathogen, the incidence and severity of illness is likely to be higher.

b. *The infection may have been acquired days or weeks before donation – e.g. HIV, HBV or HCV, WNV – and the donor has not yet developed clinical symptoms or a measurable antibody response to it.*
The time interval between exposure to a pathogen and the point when assays are able to detect specific markers of infection is known as the window period. Another phase also exists, when local replication in specific target tissues, such as lymph nodes or the liver, takes place before systemic spread, hence neither the pathogen nor an immunological response to it can be detected in the blood; this is the so-called eclipse period. In the setting of eclipse or serological window period, despite negative screening results, the use of infected organs may transfer the infection from the donor to the recipient. During the serological window period, the pathogen is present in the blood circulation, but antibodies are not detectable because humoral immune responses have not yet occurred (see Figure 8.1).
Since antibody screening assays may not be reactive during the serologic window period, and clinical signs may be absent, assessment of the pathogen in the blood by nucleic acid testing (NAT) may reduce the period between initial infection and possible detection (e.g. the window period for the detection of HCV is reduced from approximately 70 days using antibody detection to 5-7 days using NAT). However, by definition, during the eclipse phase, NAT may also fail to detect the pathogen in the blood or plasma (≈ 5-7 days for HIV and HCV, and ≈ 20 days for HBV), and infection may be transmitted even with a non-reactive NAT [17-19]. If any risk factors for recent acquisition of an infection are identified, it is mandatory to share this information with all concerned parties involved in the donation–transplantation process.

c. *The infection may have been acquired during the terminal hospital stay or contamination may have occurred during the organ procurement, transportation and storage process.*
This risk is very high for nosocomial bacterial and fungal infections, although transmission of other infections (e.g. WNV, *Babesia* spp.) through blood products has also been described [20-21]. Diagnostic systems are more limited for detecting these types of infection; for example, organs may have already been transplanted before reactive bacterial/fungal cultures become available. Assays with pending final results at the time of procurement need to be carefully recorded, and timely follow-up of all results is mandatory. Any infection or new diagnostic information should be conveyed as soon as possible to all transplant centres that have accepted organs from the affected donor.

Figure 8.1. **Timeline from infection until final seroconversion, including the eclipse period and window period**



Eclipse period	Window period	Seroconversion
• NAT (blood): not reactive • Serology: not reactive	• NAT (blood): reactive • Serology: not reactive	• NAT (blood): depends on clearance of pathogen in accordance with Options 1–4 • Serology: reactive (depends on pathogen: lifelong or may get lost over years)

NAT: nucleic acid testing.

Note that detection of a pathogen may behave similarly to NAT testing. After seroconversion the pathogen may be removed from the blood compartment, or not, while it can persist in other tissues lifelong.

Table 8.1. **Abbreviations used for the reporting of laboratory screening results**

Abbreviation (standardised)	Other abbreviation still in use	Explanation
HBsAg		Surface antigen of hepatitis B virus (HBV)
anti-HBc	HBc-Ab	Antibodies against the core antigen of HBV*
anti-HBs	HBs-Ab	Antibodies against the surface antigen of HBV
anti-HBe		Antibodies against the envelope antigen of HBV
HBeAg		Envelope antigen of HBV
anti-HCV	HCV-Ab	Antibodies against hepatitis C virus
Anti-HEV	HEV-Ab	Antibodies against hepatitis E virus
anti-HIV	HIV-Ab	Antibodies against human immunodeficiency virus (HIV)
anti-HIV-1/2	HIV-1/2-Ab	Antibodies against HIV type 1 and 2
anti-HIV-1	HIV-1-Ab	Antibodies against HIV type 1
anti-HIV-2	HIV-2-Ab	Antibodies against HIV type 2
HIV-1-p24-Ag	HIV-p24-Ag	Protein p24-antigen of HIV type 1
anti-CMV	CMV-Ab	Antibodies against *Cytomegalovirus* (CMV)*
anti-EBV	EBV-Ab	Antibodies against Epstein–Barr virus (anti-EBV-VCA and anti-EBV-nuclear antigen (EBNA) are usually tested in donors and the test used should be specified)*
anti-Toxoplasma		Antibodies against *Toxoplasma gondii*
anti-*Treponema pallidum*	Lues Ab	Antibodies against *Treponema pallidum*
anti-HTLV-1/2		Antibodies against human T-lymphotropic virus types 1 and 2
SARS-CoV-2		Severe acute respiratory syndrome – Coronavirus 2
Anti-SARS-CoV-2		Antibodies against Severe acute respiratory syndrome – Coronavirus 2 (SARS-CoV-2)
D+/R–		The donor is seropositive for the pathogen and the recipient is seronegative* (i.e. is naïve)
D+/R+		Both the donor and the recipient are seropositive for the pathogen*
D–/R+		The donor is seronegative (i.e. is naïve) and the recipient is seropositive for the pathogen*
D–/R–		Both the donor and recipient are seronegative for the pathogen*
Reactive	positive	Any 'reactive' or 'detected' test result indicates either a current or past exposure to an infectious agent. The medical community documents this as 'positive'.
non-reactive	negative	Any 'non-reactive' or 'not detected' test result only indicates that the test did not detect the specific marker in the specimen investigated. The medical community documents this as 'negative', without knowing whether the pathogen was missed or whether it was not present.

* BAL or lower airway specimen should be investigated in every lung or intestinal donor. D/R-sero status is driven by IgG-antibody status of donor and recipient. Most laboratories rely on IgG-tests for screening.

A review of the available information (e.g. case history, travel history, medical history, contacts and signs of infection) should guide the decision-making process as to which pathogens to screen for, over and above the mandatory markers, and a balanced approach is required. However, it is impossible to completely exclude all risks for unexpected disease transmission.

Some further pitfalls or limitations exist in screening for infectious diseases in organ donors:

- Because of changing epidemiology and the globalisation of geographically restricted infections, the number of infections potentially transmitted by organ transplantation exceeds the testing capabilities of laboratories. Therefore, national authorities should ensure that a national/regional epidemic surveillance service is established (usually within the national public health institution) to provide expert information on outbreaks or changes of disease epidemiology that pose a threat to human health by a potential transmission via human contacts including organ transplantation. This information about epidemiology and risk factors for donor-derived infections should be shared with organ-procurement organisations (OPOs) and transplant centres as well as with the national organ transplantation authorities, who should produce timely responses to potential threats by assessing the risk and recommending preventive interventions. In this regard, information provided by the European Centre for Disease Prevention and Control (ECDC) rapid risk assessments

or other scientific advice may be consulted. The performance, sensitivity and specificity of screening assays should be reviewed periodically. Unresolved, potentially false positive screening results, or inability to screen for relevant suspected pathogens, must be avoided in order to minimise unnecessary organ loss [7]. In this context, each OPO should regularly refer to the institutions mentioned in section 8.2 for monitoring of global changes in infections and vector monitoring. In addition, surveillance of local epidemiology requires the same process as for national and regional reports, because there may be significant differences.

- Basic screening results must be available before organ procurement (see §8.2). This tight timeline may preclude confirmatory tests for certain pathogens – e.g. false positive results in human T-cell lymphotrophic virus-1 and 2 (HTLV-1/2) screening [22].
- In deceased donors, cerebral lesions can mimic a state of generalised inflammation. Parallel to the failure of all brain-stem reflexes, a systematic inflammatory response syndrome can be observed [23], which may mimic a sepsis-like syndrome. Careful interpretation and acknowledgement of this is needed.
- In living donors, acquisition of infection between initial screening and actual organ donation can occur [24]. It is essential to ensure screening or re-screening close to the time of organ procurement and education of the potential living donor on how to avoid acquiring infections between screening and procurement [25].
- Abbreviations used in viral screening and interpretation of results should be standardised, as summarised in Table 8.1. Alternative abbreviations commonly used in the regional/national language may also be used, but with proper explanations. In order to avoid misinterpretation, test results should be communicated properly, taking into account all the limitations of screening tests as outlined above (see also §8.10.3). In that respect, written interpretation of results in the laboratory report is highly desirable.

For transmissible infection, risk assessment has shifted from dichotomous grading to an individual risk–benefit assessment taking into account all particular donor and recipient factors (see §6.1.1). Therefore, in so-called non-standard-risk donors, the clinician must determine case by case if post-exposure prophylaxis or treatment of the pathogen exists and if it is possible to apply it in the recipient without harm. Even in standard-risk donors, each donor–recipient combination must be assessed individually, based on their respective risks for infections and the risks related to spending a prolonged time on the waiting list.

8.2. Basic screening for infections in organ donors

The basic screening for infections in deceased organ donors must include the tests shown in Table 8.2, with results being provided within the time frame specified there.

Based on the regional prevalence of endemic infections, mandatory basic screening may be extended with tests listed in Table 8.3 [26].

Table 8.2. **Basic screening for infections in deceased organ donors**

Before organ procurement and/or transplant (1-3 h)	As soon as possible (not necessarily before organ procurement and transplant)	Retrospectively after transplant, if indicated at the recipient centre
anti-HIV-1/2 (incl. HIV-1-p24-Ag)† HBsAg and anti-HBc anti-HCV† SARS-CoV-2 RNA on nasopharyngeal swab or BAL*	anti-CMV IgG anti-EBV-VCA-IgG, -EBNA1-IgG anti-*Treponema pallidum*‡ anti-Toxoplasma IgG	Additional tests can be performed according to the recipient profile for targeting specific prophylaxis

Note: see also §8.2.1.

* This is a current recommendation that might change in the future according to the evolution of the pandemic.

† In donors at an increased risk for HIV or HCV infection screening should be extended to HIV and/or HCV-NAT (see §8.2.1). Any anti-HCV reactive result should be verified by HCV-NAT.

‡ Tests used: enzyme-linked immunosorbent assay (ELISA), chemiluminescence immune assay (CLIA), *Treponema pallidum* haemagglutination assay (TPHA)/*Treponema pallidum* particle agglutination assay (TPPA) or Venereal Disease Research Laboratory (VDRL)/rapid plasma reagin (RPR). The preferred tests are ELISA or CLIA, in order to omit high rate of false positive results by use of other tests. Results available pre-procurement are preferred, because reactive results might help to identify an increased risk for infection caused by other blood-borne pathogens.

Table 8.3. **Additional tests which should be considered for donors with certain geographic connections**

Test	Central & South America	North Africa	Sub-Saharan Africa	Indian sub-continent	Southeast Asia	Europe
HTLV serology§	always	always	always	always	always	Romania
NAT* for *Plasmodium* spp.	Central America and Amazon	no	always	always	always	
Stool examination†	always	always	always	always	always	
Urine examination‡	no	Egypt	always	no	no	
Strongyloides stercoralis serology	always	always	always	always	always	
Schistosoma spp. serology	Caribbean, Venezuela and Brazil	always	always	no	always	
Trypanosoma cruzi serology for screening; (NAT or Strout test for exclusion of parasitaemia)	always (not Caribbean)	no	no	no	no	
Leishmania see Table 8.8	always	always	always	always	always	
Paracoccidioides brasiliensis serology	Brazil	no	no	no	no	
Coccidioides immitis serology	always	no	no	no	no	
Histoplasma capsulatum see Table 8.8	no	no	Western Africa	no	no	

Note: The above tests should be considered for screening of donors who have lived in and/or travelled to, and/or have family relations in, those geographically restricted areas or are at risk for vertical transmission due to ancestors having lived there. Depending on the pathogen, advice after consultation of a transplant infectious disease expert and organ intended to be transplanted, the results of some tests are not needed to become available before transplantation: please refer to the section on the pathogen.

Source: modified according to [26].

* NAT is sensitive for ruling out parasitaemia, but limited availability for routine diagnostics may require other tests.

† *Entamoeba histolytica*, *Clonorchis* spp., *Opisthorchis* spp., *Schistosoma* spp., *Strongyloides* spp.

‡ *Schistosoma haematobium*.

§ Spain, France: screen regularly, other countries on indication: see §8.6.2.16.

Serological screening should be complemented with NAT for donors with an increased risk of HIV, HBV or HCV infection [5]. Such risk factors are discussed in section 8.3; and 8.2.1 provides information about the initial screening algorithm. The results of these tests must be made available before organ procurement or transplantation. However, even with NAT-negative results, these donors must still be considered at increased risk because of the residual risk posed by the eclipse period. Accordingly, recipients should be tested as described in Table 8.4 and section 8.1. Note that the risk of missing HIV, HBV and HCV infection exists in donors not thought to be at increased risk by any screening algorithm. Therefore, the United States Public Health Service (PHS) guidelines recommend that every recipient be screened for undetected donor-derived HIV or HBV or HCV infection by NAT in the intervals outlined in Table 8.4 [27].

In the event of an anti-HCV reactive result, HCV-NAT should be performed as a complementary test to assess current infectious status (spontaneous clearance, sustained virological response after therapy or falsely reactive antibody result). If NAT testing is not available, antigen test should be performed. HCV core antigen in serum or plasma is a marker of HCV replication and can be used instead of HCV RNA to diagnose acute or chronic infection. HCV core antigen assays are less sensitive than HCV RNA assays (lower limit of detection equivalent to approximately 500 to 3 000 HCV RNA IU/mL, depending on the HCV genotype) [28]. Even if a negative result for HCV-NAT is obtained, HCV may still persist in the liver tissue [29-30]. With wider use of direct-acting anti-viral drugs (DAAs) for the treatment of HCV, a large number of HCV-seropositive, NAT-negative donors will be available. Recent US guidelines [31] as well as other authors [32-33] suggest that organs from such donors can be transplanted safely if close recipient monitoring is in place. Also, several published studies in the United States and elsewhere exist, in which HCV-viraemic donor grafts are intentionally used for HCV-uninfected recipients who receive DAA pre-emptively or without delay post-transplant without serious adverse events (see §8.6.2.12) [34-40]. Therefore, the severity and consequences of HCV transmission have changed and

should be taken into account in considering the use of donors at increased risk for HCV infection.

Samples for microbiological investigations, e.g. blood cultures, broncho-alveolar lavage (BAL), urine cultures, should be taken prior to organ procurement, as indicated.

Since 2020 every donor should be screened for SARS-CoV-2 infection (see §8.6.2.19) by clinical data as well as NAT testing of nasopharyngeal swab and BAL (the latter recommended in lung donation).

Donor screening should be performed with the latest-generation assay available, according to the manufacturer's instructions and as licensed by the national health authorities [8]. Each centre should have a plan for how to handle reactive or unexpected results (see §8.2.1 and §8.10.1) [8]. For basic screening, serologic tests should detect IgG antibodies. Only in special cases is IgM detection necessary. The use of IgM for donor screening is not advocated on the basis of the little information gained and the high rate of false positive results. Donor sera or plasma samples should be stored for at least 10 years by the OPO, according to the methods available and national recommendations [7].

Screening protocols must be reviewed regularly because of the rapid development in testing repertoires. The recommendations of this Guide are based on the technology available in 2020 in most Council of Europe member states and on the basis of 24 h a day, 365 days a year availability with regard to the needs of deceased organ donation. In some countries, multiple different techniques are employed for NAT and serological testing according to their local certifications. In such cases, appropriate sensitivity, specificity and turn-round time must be ensured when using NAT testing under the specific circumstances of organ donation, i.e. as single-specimen runs outside standard working hours and without routine staff availability.

Multiplex NAT-screening assays for HIV, HBV and HCV can be used when individual donor screening (ID-NAT) is performed and if sensitivity as well as specificity is equivalent to individual NAT. Reactive multiplex NAT results must be confirmed according to manufacturer's instructions (usually by pathogen-specific NAT).

Reactive anti-*Treponema pallidum* screening should be verified by complementary diagnostics for discrimination between past and active infection.

Serologic markers may not be reactive during the window period and viraemia may not exist during the eclipse period. Further viral infections may not be detected by NAT unless a specimen has been drawn from the appropriate tissue, e.g. rabies from specific areas of the brain, cardiotropic virus from the myocardium. Therefore, organs should not be transplanted from a donor if there is strong clinical evidence or strong suspicion of an infection in the donor, especially when there are no suitable treatment options for organ recipients.

Table 8.4. **Minimum screening of all recipients for possible unexpected HIV, HBV, HCV or HEV infection after transplantation, to exclude donor-derived infection**

Recipient testing during hospital admission for transplant procedure before transplant, regardless of donor risk criteria	• HIV: according to guidelines • HBV: anti-HBc, anti-HBs and HBsAg • HCV: HCV-NAT and anti-HCV • HEV: HEV-NAT when indicated • For example: due to the current epidemiological situation in 2020/21, SARS-CoV-2 investigations according to local hospital admission guidelines must be considered
Recipient testing and vaccination before transplantation while on the waiting list	• All organ transplant candidates should receive HBV vaccination • Screening for HIV, HBV and HCV (also HEV when indicated) should be performed at regular intervals because this determines allocation criteria • For example: due to the current epidemiological situation in 2020/21, SARS-CoV-2 vaccination according to national guidelines must be considered
Recipient testing after transplantation regardless of donor risk criteria	• Type of testing: NAT for HIV, HBV and HCV – serological test may fail due to false negative results (e.g. inadequate response to produce antibodies under immunosuppression) or false positive results (e.g. due to transfer of donor passenger lymphocytes temporarily producing antibodies, unspecific reaction by (IgM) antibodies) • Timing: 4-6 weeks post-transplant (before this time has elapsed, NAT results can be false negative) • In liver recipients, maintain awareness for possible delayed appearance of HBV infection; consider additional testing for HBV-NAT at 1 year • Recipients who develop signs or symptoms of liver injury after transplantation should be retested for viral hepatitis (NAT) including HEV (In some European regions HEV infection is endemic: HEV infection is usually diet-related but transmission through blood transfusion and organ transplantation is known to occur; therefore regular recipient screening is proposed)

Note: Determinations about emerging diseases must be considered according to the most recent epidemiological situation [27, 41].

The requirements for testing of donors vary between European countries due to the variability in specific/endemic prevalence of viral diseases [2, 6, 8]. Up-to-date information about known, new and emerging, seasonally occurring or regionally endemic virus infections (e.g. WNV, Usutu, chikungunya, dengue, Zika, Yellow fever, influenza virus, SARS-CoV-2) can be obtained from the references listed below. The relevance of these data should be discussed within each member state for developing regional strategies in updating local screening algorithms.

Websites

For more specific information about infections, see:

◊ 'Travel and Health' pages at www.who.int/ith/en
◊ Centers for Disease Control (CDC) in the USA: the yellow book at wwwnc.cdc.gov/travel
◊ European Centre for Disease Prevention and Control (ECDC) at www.ecdc.europa.eu/en
◊ https://coronavirus.jhu.edu/ for SARS-CoV-2 pandemic
◊ other reference centres within member states (e.g. for Germany, www.rki.de)
◊ disease-specific websites from scientific societies (e.g. for SARS-CoV-2, www.tts.org/covid-19)

For each pathogen discussed in the following sections, the reader is advised to refer to the websites of the above-mentioned organisations, where the most current epidemiological information can be obtained.

Initial screening

Initial screening algorithms for donors at standard risk for HIV-, HCV- and HBV infection are shown in Figures 8.2a, 8.3a and 8.4.
Initial screening algorithms for donors at increased risk for HIV-, HCV- and HBV infection are shown in Figures 8.2b, 8.3b and 8.4.

NAT and diagnostic window

The use of simultaneous NAT screening for HCV and HIV decreases the diagnostic window period to a few days (HIV-1 NAT screening only, unless otherwise requested).
NAT for HBV is not necessary, except for occult HBV infection.
The utility of NAT screening in donors lacking identified risk factors is that it also decreases the diagnostic window period. However, access to NAT for prospective single donor screening is very limited in many European countries and the risk of missing an early infection may be very low.

Anti-HBc/anti-HCV results

Donors that do not present elevated risks for infection as outlined in §8.3, but are HBsAg non-reactive and anti-HBc reactive, should be considered at risk for potential HBV transmission for liver grafts (see §8.6.2.11).
In donors with anti-HCV reactive results, HCV-NAT may clarify whether the donor is viraemic or not, with relevant consequences for the use of organs (see §8.6.2.12).

8.2.1. Initial screening algorithms in organ donors for HIV, HCV and HBV

Different screening algorithms are provided (see Figures 8.2, 8.3 and 8.4), based on the recognised risk of the donor, to be without or with increased risk for HIV, HCV or HBV infection as outlined in section 8.3.

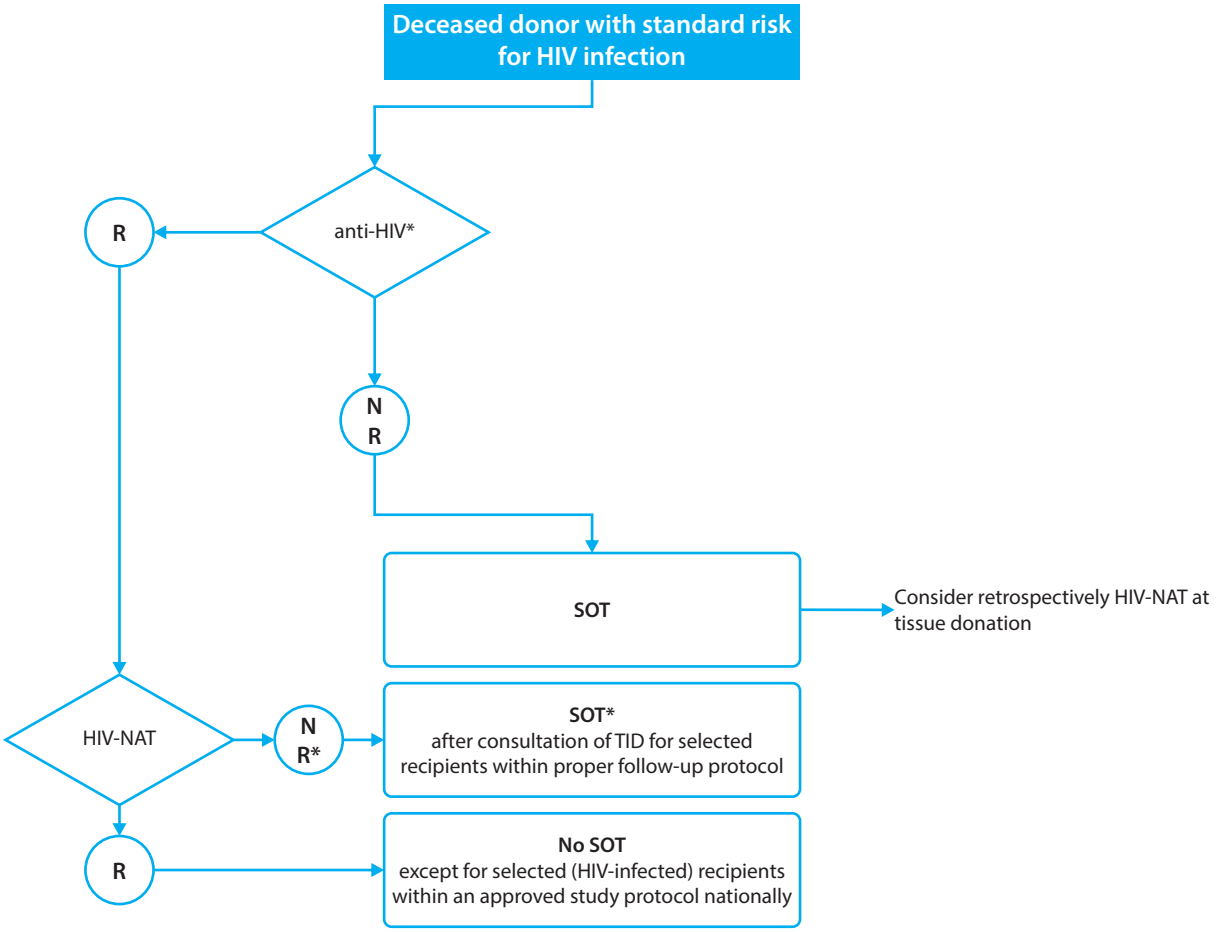
For HIV, HCV and HBV screening tests, the possibility of an initially reactive result must be considered for any organ donor. As this initial reactive result may be a true positive or a false positive, a pragmatic algorithm for verification of the initial result must be used, due to the time constraints in organ donation (see Figures 8.2, 8.3 and 8.4 for an algorithm at first initial testing). Any initially reactive result in tissue or cell donors without time constraints must be verified according to local protocols (e.g. proper handling of specimen by high-speed centrifugation and repeat double testing in cases of unexpected results).

8.2.2. Basic screening for infections in living organ donors

Basic screening should be performed at initial counselling for living organ donors, as well as at final counselling and/or before organ procurement, and results must be available before an organ is removed for transplantation. The repeat testing should be performed as close to the donation procedure as possible, the interval not to exceed 4 weeks because greater intervals have been associated with disease transmission [27, 42]. Counselling of the donor and recipient should include the information that infections may be acquired during the period from initial to final screening and up to the day of transplantation [25]. This requires education about avoiding infections like HIV, HCV, HBV and regionally endemic infections (e.g. tick-borne encephalitis), which may help to reduce risks. For further details see Chapter 13.

Figure 8.2. **Screening algorithms for HIV infection in potential organ donors**

8.2.a. Standard-risk donor



R=reactive, NR=not reactive, SOT=solid organ transplantation, ECD=extended criteria donor, TID=transplant infectious disease expert; anti-HIV=anti HIV 1/2 incl. HIV-1 p24Ag.

* It must be ensured that donor was not on active treatment for HIV with suppressed HIV (if uncertain proceed as if HIV-NAT is R). Informed consent should be obtained in any case.

Note: In the case of an anti-HIV reactive result, confirmation of the result is recommended before a donor is rejected or the organs are discarded on the basis of a result obtained through this screening algorithm. The donor hospital, donor co-ordinator and organ procurement organisation, as well as the laboratories performing investigations beyond the pathway shown here, should discuss all the options and risk-assess the situation based on an agreed protocol. For further consideration about protocols of HIV-to-HIV transplantation (D+/R+ and D+/R–), see §8.6.2.15.

8.2.3. Basic screening for infections in deceased or living tissue and cell donors

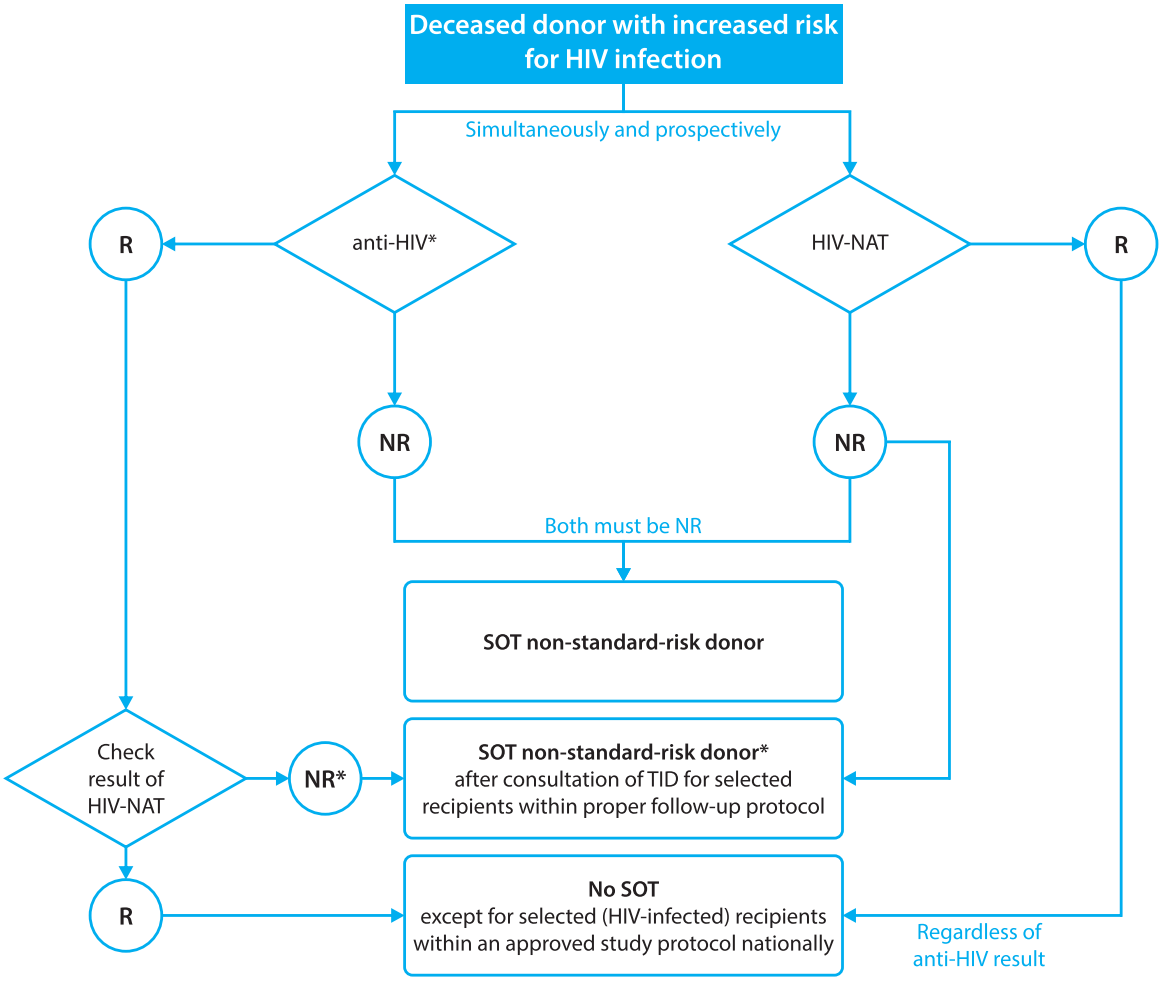
Please refer to the latest edition of the Council of Europe *Guide to the quality and safety of tissues and cells for human application*.

8.2.4. Previous vaccinations of the donor

Vaccinations with live attenuated vaccines may result in transmission of a vaccine-derived pathogen to an immunosuppressed recipient. This may give rise to a disseminated life-threatening disease. In contrast, inactivated vaccine or passive immunisation of the donor is unlikely to pose harm to the recipient, but may confound screening testing in paediatric donors.

Therefore, it is imperative to determine if the donor has received live vaccines during the previous 4 weeks. Live vaccines include: inhaled, attenuated influenza (not injectable, inactivated influenza), varicella–zoster (VZV; except for recombinant subunit VZV vaccine [43]), rotavirus (below 6 months of age), measles, mumps, rubella, bacillus Calmette–Guérin (BCG), smallpox, oral cholera (not injectable), oral polio (not injectable), yellow fever or oral *Salmonella typhi* (not injectable). In this case, an individual risk assessment of the immune status of all prospective recipients is mandatory.

8.2.b. Increased-risk donor



R=reactive, NR=not reactive, SOT=solid organ transplantation, ECD=extended criteria donor, TID=transplant infectious disease expert; anti-HIV=anti HIV 1/2 incl. HIV-1 p24Ag

* It must be ensured that donor was not on active treatment for HIV with suppressed HIV (if uncertain proceed as if HIV-NAT is R). Informed consent should be obtained in any case.

Note: In the case of an anti-HIV reactive result, confirmation of the result is recommended before a donor is rejected or the organs are discarded on the basis of a result obtained through this screening algorithm. The donor hospital, donor co-ordinator and organ procurement organisation, as well as the laboratories performing investigations beyond the pathway shown here, should discuss all the options and risk-assess the situation based on an agreed protocol. For further consideration about protocols of HIV-to-HIV transplantation (D+/R+ and D+/R–), see §8.6.2.15.

Conclusion

Note that, for the currently available SARS-CoV-2 vaccines (mRNA, non-replication viral vectors, protein subunit and inactivated based vaccines), the 4-week time interval prior to donation does not have to be respected.

If the donor has been vaccinated in the last 4 weeks pre-donation with live vaccines, a risk assessment should be carried out and the recipient should be monitored post-transplant because there is the risk of transmission of an acute infection by a live attenuated vaccine.

Live vaccines include vaccination against the following pathogens:

◊ Influenza (inhaled = live, injectable = inactivated)
◊ Varicella, including VZV except subunit VZV vaccine
◊ Rotavirus
◊ Measles
◊ Mumps
◊ Rubella
◊ BCG
◊ Smallpox
◊ *Vibrio cholerae* (oral = live, injectable = inactivated)
◊ Yellow fever
◊ *Salmonella typhi* (oral = live, injectable = inactivated)
◊ Polio (oral = live; injectable = inactivated)

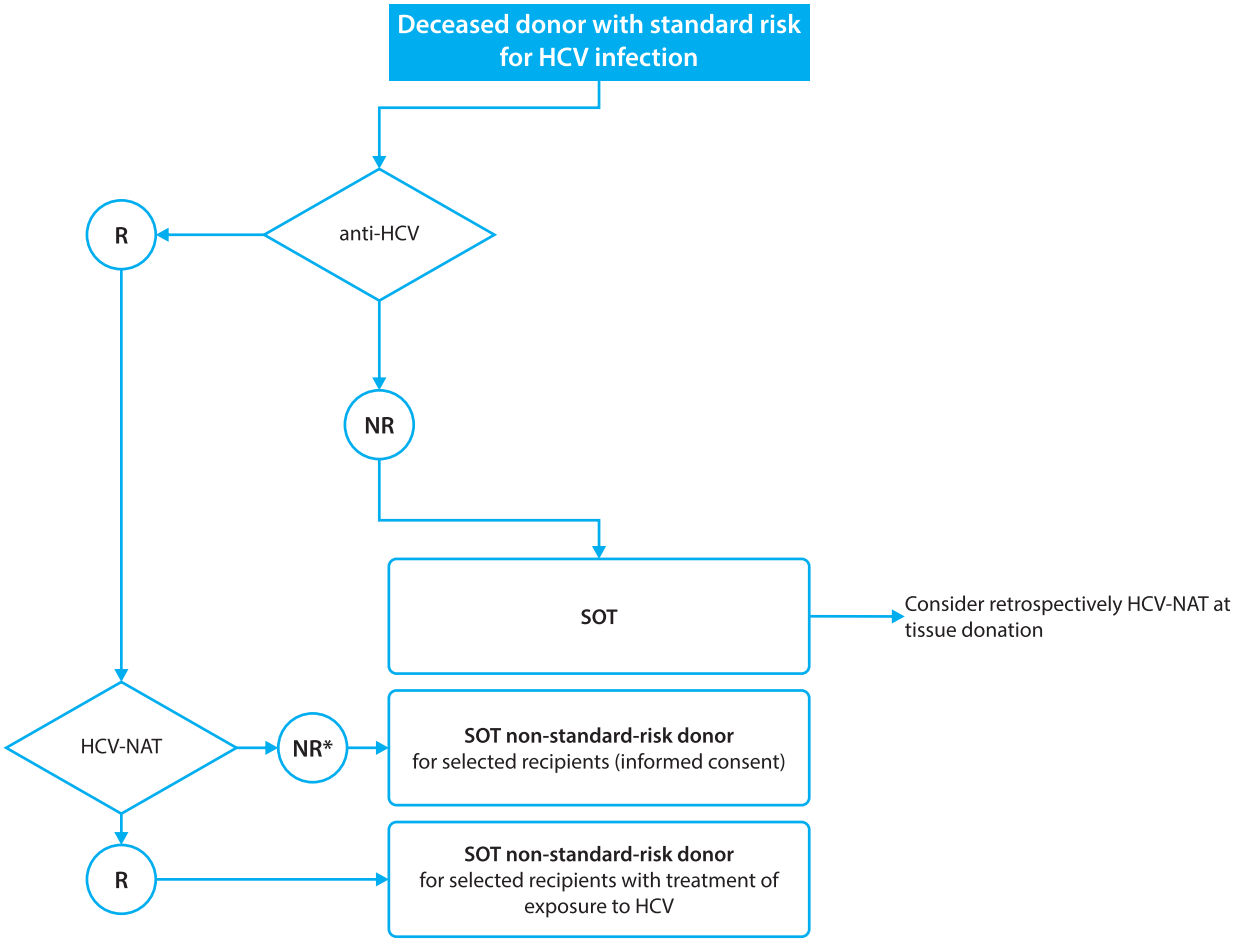
For some vaccines, the risk of transmission is limited to specific organs:

◊ Inhaled influenza vaccine: lung, face
◊ Rotavirus: intestine
◊ Cholera: intestine
◊ *Salmonella*: intestine

For the currently available vaccines against SARS-CoV-2 infection based on mRNA, non-replication viral

Figure 8.3. **Screening algorithms for HCV infection in potential organ donors**

8.3.a. Standard-risk donor



R=reactive, NR=not reactive, SOT=solid organ transplantation. ECD=extended criteria donor.

* Consider ongoing HCV treatment without sustained virological response or spontaneous clearance as if HCV-NAT is R.

Note: In the case of an anti-HCV reactive result, confirmation of the infectious status by NAT is desirable before a donor is rejected or the organs are discarded on the basis of a result obtained through this screening algorithm. The donor hospital, donor co-ordinator and organ procurement organisation, as well as the laboratories performing investigations beyond the pathway shown here, should discuss all the options and risk-assess the situation based on an agreed protocol. For details about HCV infection in donors, see §8.6.2.12. Some European countries will perform retrospective HCV-NAT testing.

vectors, protein subunit and inactivated virus, there is no risk for the recipients and therefore there is no need to respect the pre-donation 4-week time interval. As an exception, donors with severe vaccine-induced complications should be evaluated on a case-by-case basis and with expert advice.

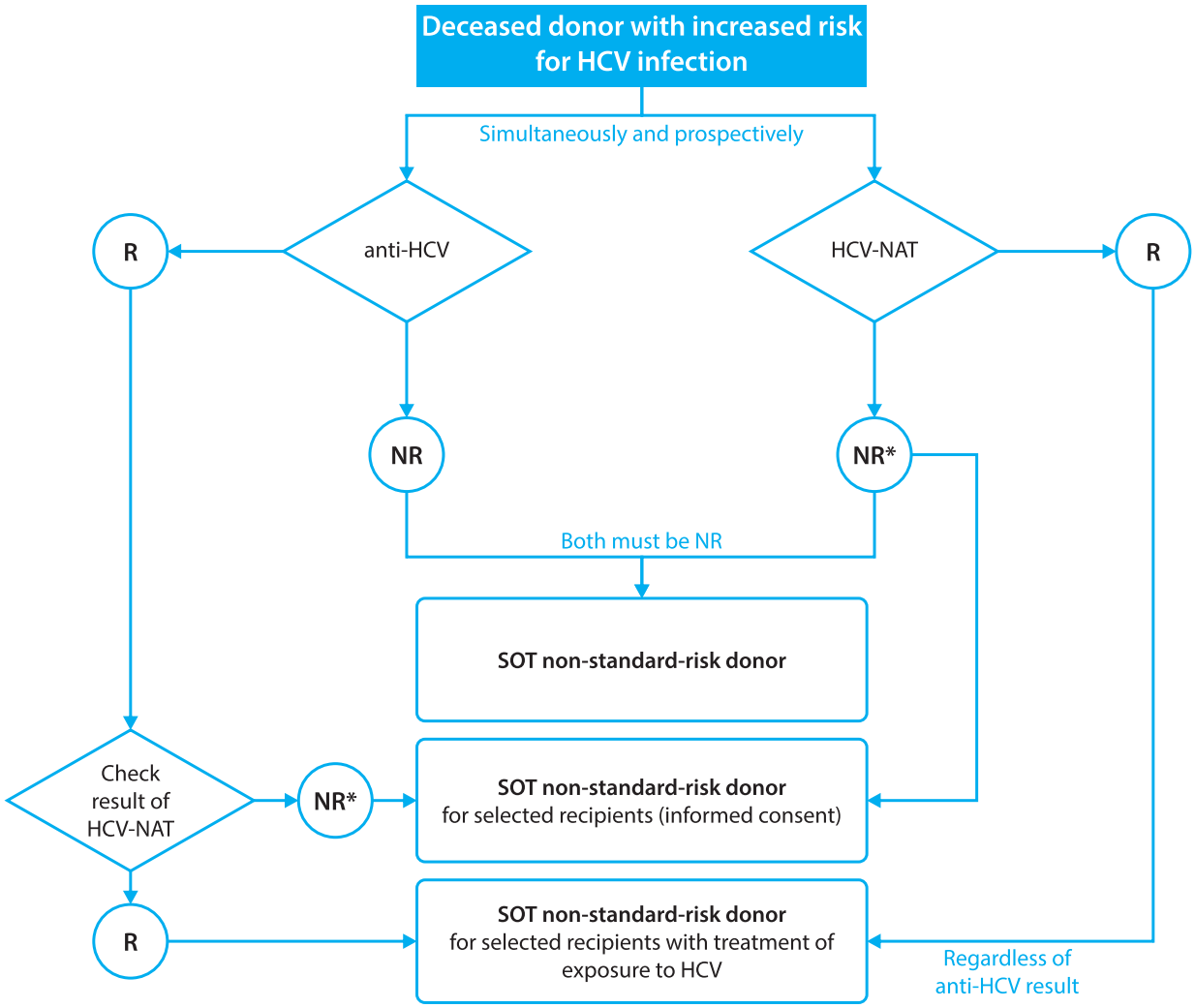
8.3. Medical and behavioural history to inform consideration of the risks of infection and implications for screening

Guidelines on risks of transmission of infections are based on donor history and behaviour history. They vary between countries and regions due to different local disease prevalence and risk assessments. They should be regularly reviewed regarding epidemiological changes and diagnostic developments.

Data to be obtained for detecting potential infectious disease-transmission risks are outlined in section 6.2 as well as appendices 10, 11 and 13.

One major concern is the risk of unintended transmission of HIV, HCV or HBV infection [27]. The incidence and prevalence of HIV and HCV infection varies, depending on different risk factors [44-50]. Furthermore, the causes of such *de novo* infections vary between European regions [46]. Unfortunately, there are only a few studies based on adequate evidence that define the risks of window-period infections in organ donors [19, 27]. Where such studies exist, data cannot be directly extrapolated from one

8.3.b. Increased-risk donor



R=reactive, NR=not reactive, SOT=solid organ transplantation, ECD=extended criteria donor.

* Consider ongoing HCV treatment without sustained virological response or spontaneous clearance as if HCV-NAT is R.

Note: In the case of an anti-HCV reactive result, confirmation of the result is desirable before a donor is rejected or the organs are discarded on the basis of a result obtained through this screening algorithm. The donor hospital, donor co-ordinator and organ procurement organisation, as well as the laboratories performing investigations beyond the pathway shown here, should discuss all the options and risk-assess the situation based on an agreed protocol. For details about HCV infection in donors, see §8.6.2.12.

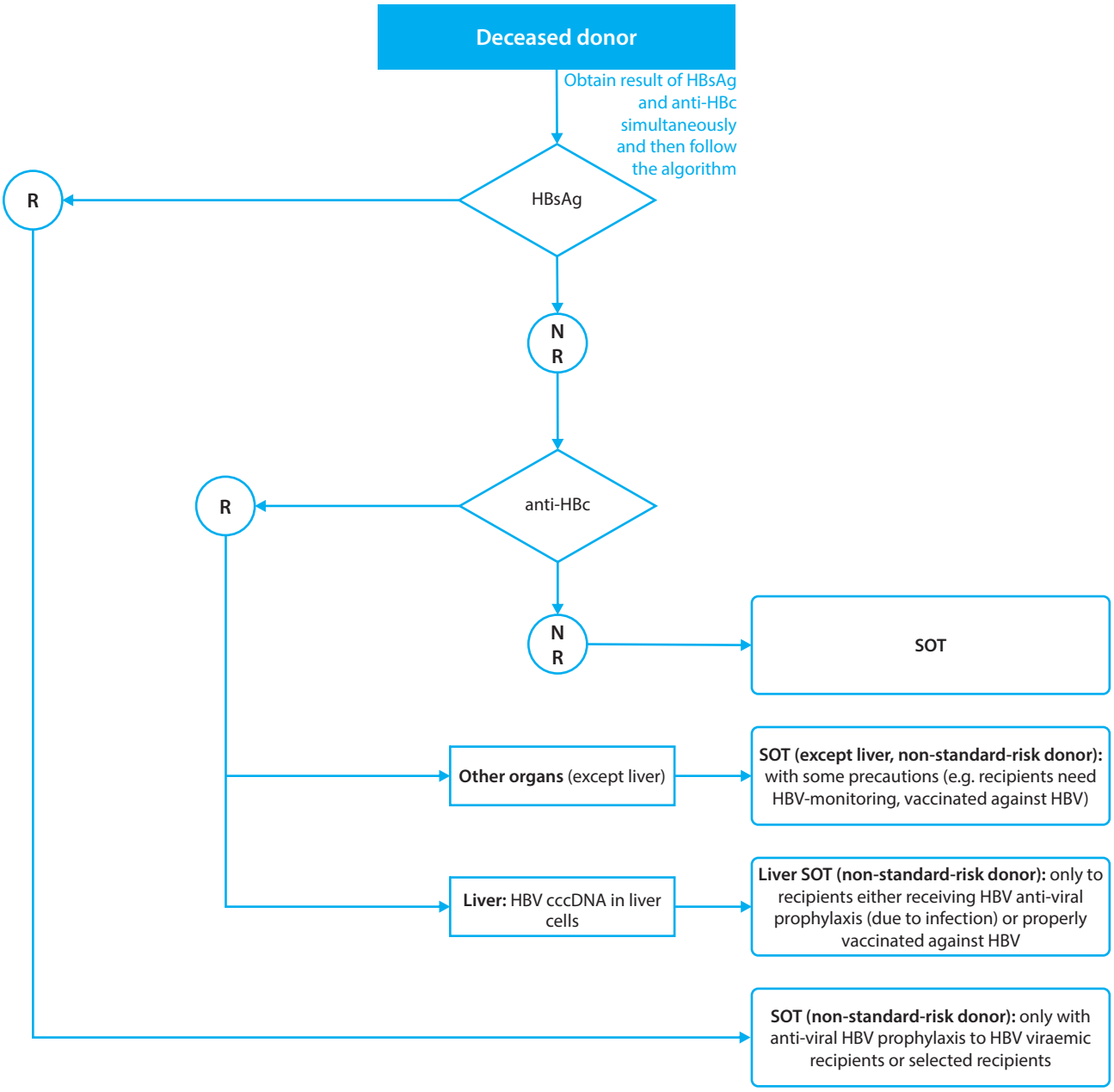
population to another because the variables used for calculations differ.

In spite of these limitations, the evidence-based guidelines issued by the US Public Health Service (PHS), as updated in 2020, are recommended for assessing individuals at risk for HIV, HCV or HBV infections [27]. According to these guidelines, donors should be considered at risk for HIV, HCV or HBV infections if one of the following risk criteria exists during the 30 days before organ procurement when NAT-screening is performed prospectively [27]:

- Sex (i.e., any method of sexual contact, including vaginal, anal or oral) with a person known or suspected to have HIV, HBV or HCV infection
- Man who has had sex with another man (MSM)
- Sex in exchange for money or drugs
- Sex with a person who had sex in exchange for money or drugs
- Drug injection for nonmedical reasons
- Sex with a person who injected drugs for nonmedical reasons
- Incarceration (confinement in jail, prison or juvenile correction facility) for ≥ 72 consecutive hours
- Child breastfed by a mother with HIV infection
- Child born to a mother with HIV, HBV or HCV infection
- Unknown medical or social history

In the US, screening by NAT for HCV has been mandatory since 2017, regardless of the risk criteria

Figure 8.4. **Screening algorithms for HBV infection in potential organ donors**



R = reactive, NR = not reactive, SOT = solid organ transplantation, cccDNA: covalently closed circular DNA cccDNA of HBV integrated into genome.

Note: In Figure 8.4, the screening algorithm for donors with increased risk for HBV infection is equivalent to the one for donors at standard risk for infection. Accurate communication of the risks is required. The possibility should be considered that, depending on the prevalence of HBV mutants, the testing algorithms might miss HBsAg reactivity in some populations – depending on the country where infection occurred – and hence laboratories should select appropriate testing platforms. Such cases should be discussed with a transplant infectious disease expert for proper indication of additional testing (e.g. if HBV-NAT is available, then measurement in liver tissue and blood may provide more specific information). In the case of an HBsAg or anti-HBc reactive result, confirmation of the result may be preferable before a donor is rejected or the organs are discarded on the basis of a result obtained through this screening algorithm. The donor hospital, donor co-ordinator and OPO, as well as the laboratories performing investigations beyond the pathway shown here, should discuss all the options and risk-assess the situation based on an agreed protocol. For details of HBV infection in donors, see §8.6.2.11. In the case of an HBsAg+ result, exclude HDV infection (see §8.6.2.13).

identified during screening, to reduce the diagnostic window period [5, 27, 51-52].

In the European setting, some considerations should be noteds:

a. In the annual epidemiological report of the European Centre for Disease Control (ECDC) [44], HBV, HCV or HIV infection is reported to be transmitted by heterosexual contacts, MSM, injecting drug abuse, medical procedures (e.g. chronic haemodialysis) or vertically, with a substantial variation in each geographic region or subpopulation of migrants and ethnic mi-

norities. Until 2019 a difference between infection rates and donors with risk factors existed in some European countries compared to other countries (e.g. [27, 44, 47-50]).

b. In contrast to the US, in most European countries NAT screening is not performed prospectively in every donor. It is best practice to do this in donors who are at increased probability for such infections (see §8.2). For pragmatic reasons the above-mentioned time range may be increased to two window periods for obtaining a reactive result after seroconversion for HBV, HCV and HIV infection in order to find a cut-off for the indication to perform NAT prospectively or not. In some countries, retrospective testing of every donor by HCV-NAT is planned; in some European countries, all tissue donors are screened by NAT.

Any recipient, particularly those having received organs from increased-risk donors, should be screened for early detection of donor-derived infections, with initial serial testing performed as outlined in Table 8.4. Frequently, recipients who acquire donor-derived infections, particularly HCV, may not seroconvert due to immunosuppression; hence, screening should always include a direct measure of the virus (i.e. NAT or antigen detection). Of note, serologic testing may be temporarily false positive due to transient activity of donor passenger lymphocytes.

Beyond basic universal screening as outlined in Table 8.2, extended testing for other pathogens (e.g. Chagas disease, malaria, *Strongyloides stercoralis*) should be considered according to specific donor risks, such as geographically restricted infections, some outdoor activities, exposure to zoonosis, insanitary living conditions etc. (see Table 8.3). Furthermore, the risk of vertical transmission from mother to child should also be considered when evaluating such issues.

As part of surveillance, vigilance and epidemiology, the occurrence of epidemic diseases in animals should be cross-checked with those of humans by public health bodies because this will help to develop preventive strategies at an earlier stage (e.g. WNV) as well as provide up-to-date information to donor co-ordinators.

The history of recent immunisations with live vaccines should also be assessed (see §8.2.4). If the donor has been previously deferred from blood donation, then the reason for deferral should be evaluated.

8.4. Bacterial infections

8.4.1. Acute infections

In accordance with standard good clinical practice, intensive care units (ICUs) monitor patients – regardless of their being a potential organ donor or not – for bacterial infections, with special attention to multidrug-resistant (MDR) micro-organisms (see §8.4.5) [53-55]. Before administering antibiotics, a culture or smear should be taken from the site of infection or target area for identification of the pathogen, and a suitably effective antibiotic agent should be validated. Antibiotic treatment should be based on determination of the pathogen/subtype and resistance pattern. Appropriate follow-up cultures should be obtained to demonstrate that the infection is under control: urine-, tracheal- and blood-cultures should be taken [56] even if final results may not be available until after transplantation of an organ. In cases of an assumed, uncertain infection, microbiological work-up of central venous access lines, etc. may be helpful. The OPO should have clear policies and procedures for following up results of any outstanding test made prior to procurement and should ensure that, when available, results are efficiently communicated to all recipient centres.

Some transplant centres routinely take smears from the abdomen or thoracic cavity or from bronchial-alveolar lavage (BAL) during organ procurement, as well as from the organ preservation solution before transplantation [57]. Investigations should cover bacteria and fungi, as well as analysis of resistance patterns.

Most positive bacterial cultures or microbiologic assays lead to a diagnosis [4, 58]. However, active infection has to be differentiated from colonisation, which may not require treatment, but could influence prophylactic antibiotic selection for the recipient. Knowledge of the local, epidemiologic background (at hospital level) helps to evaluate risks, to select appropriate antibiotics and to detect shifts in nosocomial flora and resistance patterns. If there is no apparent infection or specific indication, the use of prophylactic antibiotics is not recommended. If bacterial infection is detected, therapy must be initiated as soon as possible. Therapy should be continued until inflammation parameters are indicative of remission or until serial cultures confirm clearance of infection. However, it must be remembered that, in brain-dead donors, inflammation parameters may rise exponentially in relation to the event of terminal brain-stem coning.

Donors with bacteraemia may be accepted if appropriate antibiotics have been utilised for at least

48 h (some countries consider 24 h as sufficient) and if recovery from signs and symptoms of infection is demonstrated. Nevertheless, antibiotic treatment for a longer period may be necessary (e.g. for endocarditis). Treatment of the recipient for an appropriate duration post-transplant is strongly recommended, with careful attention to evidence of embolic infection. Organs from bacteraemic donors should be accepted on a case-by-case basis, in direct consultation with the transplantation team for appropriate post-transplant care and monitoring. The focus (organ) of such infections should not be transplanted. Bacterial growth from blood cultures may be due to contamination and not true infection (e.g. coagulase-negative *Staphylococcus*).

Localised infections without systemic spread do not contraindicate donation [7], but antibiotic treatment should be given for more than 24-48 h or until full recovery from signs and symptoms of infection has taken place. In these situations, use of a previously infected organ may be considered [7], but this should be confirmed by sterile cultures. Continuation of antibiotic treatment in the recipient should be considered. Note that an organ-specific assessment of the previously infected organ should reveal no significant damage (see Chapter 7).

Colonisation by MDR bacteria is not a contraindication for organ procurement as long as the colonised tissue remains sealed from the rest of the body, i.e. trachea or external wounds. In some cases (e.g. *Pseudomonas* or *Acinetobacter*), infection should not be confused with colonisation. Such colonised tissues and their adjacent organs may not be used for transplantation due to the risk of donor-derived pathogen transmission. Transmission of MDR bacteria has been demonstrated even when appropriate therapy was given to the donor and continued for a 2-week course in the recipients. Therefore, recipients of organs from donors with confirmed MDR organism infections require special attention, with adequate therapy and close post-therapy monitoring.

When *Aggregatibacter aphrophilus* (formerly *Haemophilus aphrophilus* and *paraphrophilus*), *Aggregatibacter actinomycetemcomitans* (formerly *Actinobacillus actinomycetemcomitans*), *Cardiobacterium hominis*, *Eikenella corrodens*, *Kingella kingae*, *Streptococcus viridans* or *Staphylococcus aureus* (MRSA) is detected in blood culture, then endocarditis should be ruled out (see §8.4.2).

Translocation of intestinal bacteria may occur in patients without enteral nutrition. Feeding via a nasogastric/duodenal tube using uncontaminated fluids decreases this possibility.

During organ procurement, inappropriate ligation of intestinal vessels may cause translocation of bacteria. Opening of the trachea or gastro-intestinal tract should be avoided or, if necessary, should take place as the very last step during procurement so that other organs or tissues are not contaminated.

Bacterial infections are a frequent problem in donors and, although there is only a low rate of donor-to-recipient transmission, significant morbidity and mortality may result when it occurs [59]. This is particularly true in the case of MDR pathogens.

Organs with active bacterial infections limited to the organ should not be used unless adequate antibiotic therapy of at least 24-48 h has been initiated in the donor and, subsequently, in the recipient. In this context, bacteraemia must be considered as an active bacterial infection affecting all organs.

8.4.2. Bacterial sepsis, -meningitis, -endocarditis and -osteomyelitis

Although organs from bacteraemic donors can be transplanted without complications if appropriate anti-microbiological agents are applied in the post-transplant recipient [4], the following issues should be considered:

a. Bacteraemia due to nosocomial pathogens (e.g. multidrug-resistant *Enterococci*, *Staphylococci* (MRSA), *S. pneumoniae*, *Pseudomonas* spp., *Escherichia coli*, *Serratia* spp., *Acinetobacter* spp. and *Klebsiella* spp. or other ESBL-producing *Enterobacterales*) is often related to the use of intravenous access and other medical support systems [1, 4]. Following transplantation, these pathogens can cause serious infections, particularly at anastomotic sites, by colonising fluids and by forming abscesses or mycotic aneurysms [1, 4]. Despite negative blood cultures, infections may be transmitted in cases of unsuspected endocarditis or pneumonia (e.g. *S. pneumoniae*). Even with transmission, most patients survive whenever effective specific antibacterial therapy is available and administered for a sufficient time.

b. The use of organs from donors with endocarditis remains controversial because of the risk of metastatic infection, although they may be used at the discretion of the transplant centre. Treatment of the recipient is highly recommended [60].

c. Donors with ongoing sepsis (and positive blood cultures) should not be accepted, especially if effective therapy cannot be confirmed. However, grafts from donors without sepsis, but with incidentally-detected bacteraemia,

have rarely resulted in disease transmission under correct antibiotic prophylaxis in the recipient.

d. If it is impossible to have the results of blood cultures available, despite treatment in the donor having been started 24-48 h before organ donation and when clinical data suggests therapy is effective, then the case should be discussed with a transplant infectious disease specialist before the donor is discarded. In most cases a preliminary result becomes available. Some specialists consider at least 24 h of appropriate treatment based on the antibiogram acceptable. It is always recommended that the same treatment be continued in the recipients until the final results of the blood cultures collected immediately before organ procurement are available. In cases of sepsis, organ damage should be carefully evaluated.

e. After recovery from septic shock or sepsis, some organs can be damaged temporarily or irreversibly or a focus of infection may persist locally. At this stage the focus of sepsis is identified and the bacterial spread eradicated, which should be confirmed by all data needed anyway for donor-specific and organ-specific assessment, including subsequent analysis for organ selection (see Chapter 7); localised foci should be considered as outlined below.

f. Continuing antibiotic treatment in the recipient according to the microbiological data of the donor should be planned for, with consultation of the transplant infectious disease expert in charge of the recipient.

There is significant evidence that donors with proven bacterial meningitis caused by *N. meningitidis*, *S. pneumoniae* or *Haemophilus influenzae* can safely be used, even if bacteraemic, as long as the bacteria are confirmed to be susceptible to the antibiotics used to treat the donor [6-7]. Optimally the donor should be treated for 48 h prior to donation [6-7], although many experts consider 24 h of active therapy to be sufficient to consider donation. Recipients should undergo treatment for the infection post-transplant. In some cases of bacterial meningitis, successful treatment can be confirmed even if bacterial growth of liquor cultures fails. When in such cases the pathogen can be identified by polymerase chain reaction (PCR), this will provide sufficient information about the infection. Meningitis caused by *Listeria monocytogenes* may disseminate systemically. Treatment by targeted antibiotics is possible, but management of immunosuppressed patients with *Listeria monocytogenes* infection is troublesome and can lead to non-acceptance of such donors by recipient centres.

In the case of an osteomyelitis, systemic spread must be ruled out.

In the case of an endocarditis, still ongoing systemic spread must be ruled out.

Generally, organs should only be considered for use after 24-48 h of targeted and effective antibiotic therapy as well as appropriate evidence of clearance of the infection. After evaluation of the case with a transplant infectious disease expert regarding the option of effective treatment in the recipient, the time interval may be shortened.

8.4.3. Pulmonary infections

Most deceased donor candidates require emergency intubation. Aspiration and consequent pneumonia must be ruled out and treated [6]. Coincident with the amount of time spent in an ICU, the rate of confirmed bronchopulmonary infections increases from 10 % to 40 % [7]. Following at least 48 h of effective antibiotic treatment and unimpaired pulmonary function, lungs (or at least unaffected lobes) may be considered for donation [7]. Transmission of MDR bacteria or fungi by colonisation of the lungs should be ruled out. Tissue biopsies of transplanted lungs may document pathogens not previously detected in BAL. If adequate antibiotic therapy according to the resistance pattern of the isolates is provided, lung recipients should not suffer complications due to donor-derived bacteria, as long as the transmitted pathogens are not MDR [61].

In the case of pneumonia without bacteraemia, all other organs can be used safely for transplant. Lungs may be used after adequate and effective antibiotic therapy of pulmonary infections.

8.4.4. Urinary tract infections

Urinary tract infections (UTIs) and pyelonephritis are common due to bacteria ascending along the urethral catheter [6]. A UTI may be considered cured after adequate antibiotic treatment (48 h in duration), but a final decision should be taken at the time of organ procurement. Post-transplant treatment of the recipient may reduce the risk of donor-derived infection. In case of a UTI restricted to the lower urinary tract, kidneys may be used as they are not infected.

In the case of UTI without bacteraemia, all other organs can be safely used for transplant. In most

cases, uncomplicated UTI/bacteriuria is not a contraindication for the use of kidneys if adequate antibiotic treatment is given to the donor and/or recipient. Any suspected UTIs in donors should be confirmed by urine culture.

8.4.5. Multi-drug-resistant bacteria

An increasing number of patients admitted to ICUs are exposed to infections with MDR organisms, in particular ESBL-producing *Enterobacterales*, carbapenem-resistant *Acinetobacter baumannii* (CRAB), *Klebsiella pneumoniae* (CR-KP) and other carbapenem-resistant *Enterobacterales* (CRE). Carbapenem-resistant Gram-negative bacteria are of particular concern because of their difficulty to treat which, in turn, results in significant morbidity and mortality, particularly among solid-organ transplant recipients [62-64]. No specific donor risk factor can predict the infection or colonisation by MDR organisms. Prolonged (> 7 days) ICU stay, vasopressor use and need for cardiopulmonary resuscitation have all been reported as independent risk factors for predicting potentially infected donors [65]. However, others have demonstrated that a period of hospitalisation as short as 2 days is, unfortunately, long enough to acquire an MDR nosocomial pathogen that can be transmitted through transplantation [66].

Anecdotal reports suggest that, with prolonged treatment after transplantation, recipients of organs from donors with MDR infection may have a favourable outcome [67]. In addition, the current availability of new drugs with activity against some MDR pathogens might allow in the future a more liberal use of organs from donors with CRE, CRAB or *Pseudomonas aeruginosa* [68].

The very limited available experience suggests that, in well-defined conditions, organs from donors who are CRE- or CRAB-positive, in respiratory secretions or rectal swabs, may be considered for transplantation. Close recipient follow-up is mandatory in order to validate this approach. In this setting, it seems prudent that lung transplantation should not be performed if the lungs are colonised. Similarly, if the donor has a positive urine culture for CRE or CRAB, transplantation of the kidneys should be avoided. However, it appears that the transplant of all other organs could be permitted.

In the presence of MDR bacteraemia, transplant of any organ should not be considered, because outcomes in such circumstances are still unknown and because the accumulated literature deals with different types of organism. In any case, consultation of the transplant infectious disease expert is strongly recommended before discarding the potential donor.

8.4.6. Tuberculosis

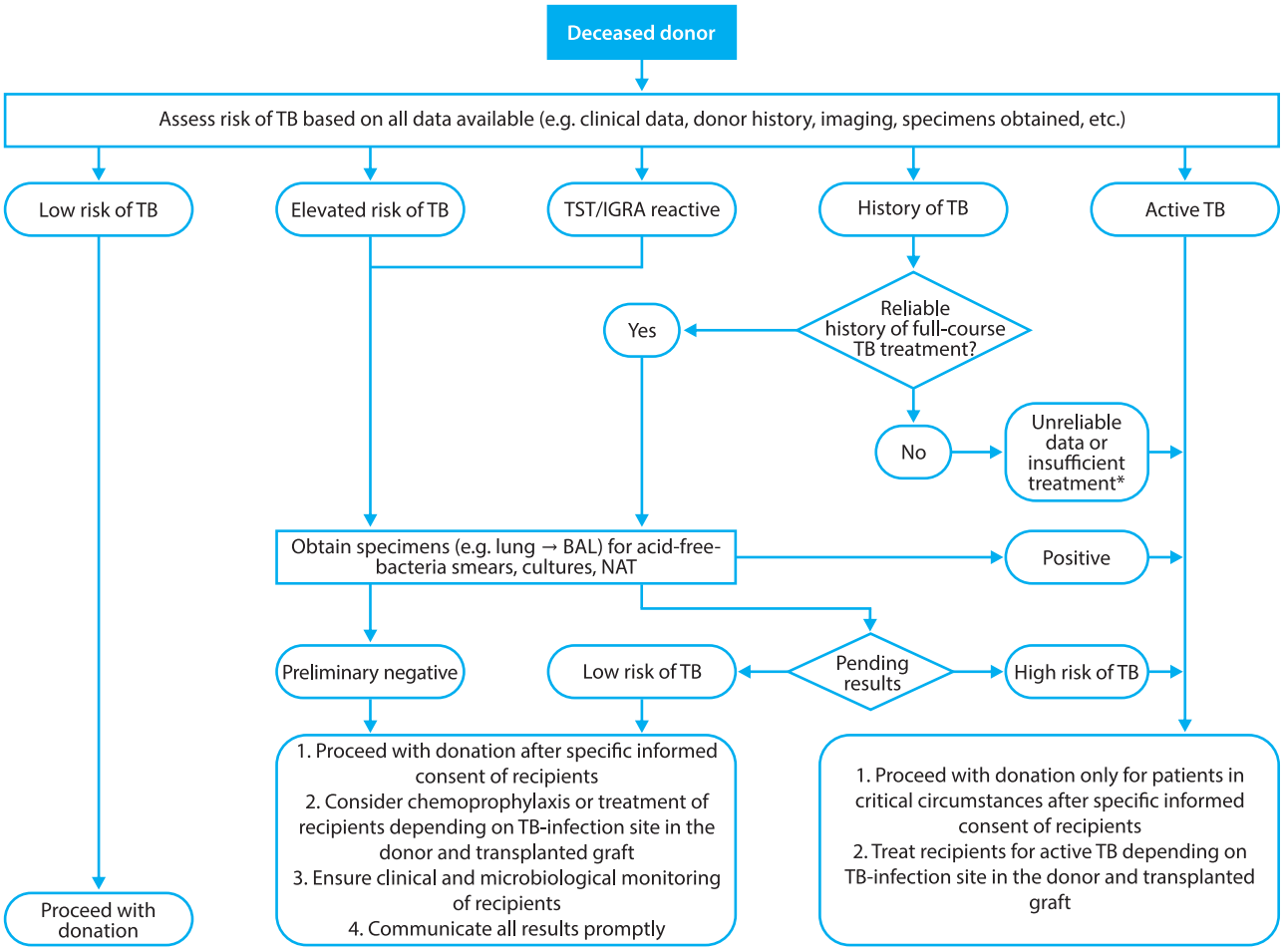
Late infections by *Mycobacterium tuberculosis* are troublesome for recipients [1, 4, 7]. Organs from donors with active tuberculosis (TB) or disseminated TB should not be utilised [69]. Organs from donors with a history of TB and with successful treatment for at least 6 months have been transplanted with success. Then treatment of latent TB infection (LTBI) of the recipient should be considered in such cases, according to the guidelines [70].

Whereas in living donation evaluation of the donor can be performed according to the recommended guidelines, in deceased donation this is challenging [70-73]. There are no proven methods for screening deceased donors for TB, but interferon-gamma release assays (IGRAs) may be helpful, although not validated for this purpose, and they may fail because of modified cellular immunity [74] due to the event of brain-stem coning. Donors who have travelled to, or previously lived in, regions with high rates of TB may be at higher risk of transmitting infection or having LTBI. In such cases, monitoring or treatment of the recipient for LTBI should be considered. Donors suffering from meningitis caused by *M. tuberculosis* may only be considered in exceptional circumstances because dissemination of TB must have occurred for infection to be localised to the central nervous system. Donors with residual pulmonary lesions can donate other organs [70-73]. For lung donors, histopathological and microbiological studies should be performed to rule out active infection (e.g. BAL for acid-fast staining smear, culture and PCR) [70-73]. Since the global prevalence of TB changes annually, in many countries it is recommended to check the WHO web page for further information (see www.who.int/tb/data).

For assessment of the risk of TB transmission in detail, refer to the consensus conference report of the American Society of Transplantation, the Canadian Society of Transplantation and The Transplantation Society [71]. In summary, the following considerations are important in deceased donors:

a. Stratify into low, moderate or increased risk of LTBI or active TB according to:
   i. country of prior residence and/or exposure (epidemiological history);
   ii. social risk factors (homelessness, incarceration, alcohol, known TB-contact, refugee camp);
   iii. medical factors (history of untreated or insufficient treatment, especially for the high risk of relapse in the past two years; investigative imaging with evidence for prior TB – especially chest X-ray and upper lung lobes; lymph nodes; cachexia; BMI < 18 kg/m^2 in adults; diabetes

Figure 8.5. **Algorithm for management of deceased donors for suspected risk of infection with tuberculosis**



* Obtain proper specimen to confirm diagnosis and communicate results promptly.

Source: adapted from Morris MI, Daly JS, Blumberg E *et al.* Diagnosis and management of tuberculosis in transplant donors [71].

mellitus; cigarette smoking; immunocompromised, reactive IGRA or other TB-screening test); and

iv. organ (consider extra-pulmonary manifestation in immunocompromised donors; check for unexplained apical fibrosis during lung procurement).

b. In donors at moderate risk, be sure not to miss active TB or disseminated TB.

c. Obtain a specimen for testing of mycobacteria (e.g. BAL, urine in suspected genito-urinary TB for NAT etc.). There are often pending results when procurement is performed. Therefore ensure that all data are forwarded as soon as they become available so it can be decided whether therapy, chemoprophylaxis or surveillance in the recipient will be appropriate for mitigation of risk.

d. Perform risk–benefit assessment according to the pathway provided in Figure 8.5. It is helpful to distinguish between grafts that are remote from the active TB-site and those affected by the active TB-site.

e. Targeted imaging studies are recommended in cases of suspected or documented past TB.

All recipients documented to have LTBI should receive treatment to prevent reactivation pre- or post-transplant. The problem of MDR TB may complicate treatment of recipients.

Active, disseminated tuberculosis is a contraindication for organ donation. Organs from donors with a history of tuberculosis may be used if successful treatment has been carried out for at least 6 months.

8.4.7. Other bacterial infections

Treponema pallidum infection is detectable by standard serology [7]. Donors with an initially reactive screening result should have infection confirmed or excluded by a *Treponema*-specific test because false positive rates are high; if reverse screening is

utilised, confirmation of positive initial results is also recommended [75]. Results available pre-procurement are preferred, because reactive results might help to identify an increased risk for infection caused by other blood-borne pathogens. Generally, organs from donors with newly diagnosed syphilis can be safely used if the recipient is treated, because latent syphilis appears not to be transmitted in this case [6]. Follow-up testing for syphilis transmission should be conducted. Any newly diagnosed syphilis should raise concerns about an increased risk for HIV, HBV or HCV infection in the window period.

For bacteria that cause infections that are commonly known as 'tropical diseases', many of which now exist in Europe (for example, leptospirosis), the basic considerations mentioned below for parasites (see §8.7) apply.

Intestinal infection by *Clostridioides difficile* has not yet been reported to be an issue in organ donation, although it is an important consideration for immunocompromised patients.

Infections by *Coxiella burnetti* (Q fever) are possible in many European regions and may be transmitted by substances of human origin. A case of Q fever transmission following bone marrow transplant has been reported. Donors presenting with symptoms such as fever, pneumonia and/or hepatitis, and association with local outbreaks or farming activities, should elicit further investigations.

Infections by non-tuberculous mycobacteria exist, but no donor-derived transmission has been reported yet.

In immunosuppressed patients (e.g. lung transplant recipient), fatal hyperammonaemia can be caused by disseminated infection of *Ureaplasma* species. Although the pathogen is typically restricted to the urinary tract, transmission from donor to recipient has been documented [76]. Whenever hyperammonaemia in a lung recipient is detected, infection by *Ureaplasma* species should be considered and tested for; alternative causes should also be looked for in non-lung recipients because *Ureaplasma*-associated hyperammonaemia is far more rare in non-lung recipients. Since the mollicutes (*Ureaplasma* and *Mycoplasma* species) lack a cell wall, special cultures, NAT screening and further tests will be required for diagnosis [77-80]. Treatment, typically with a combination of a fluoroquinolone, a tetracycline or a macrolide antibiotic, should be given with suspected infection *Ureaplasma* or *Mycoplasma* species.

8.5. Fungal infections

Disseminated fungal infections (or fungaemia), confirmed by blood cultures, must be eradicated before donation [4, 6]. For localised infections, a case-by-case consideration is necessary; for example, the trachea is often colonised by *Candida* spp.

Undetected fungal infections are a concern for lung transplant, so BAL during bronchoscopy prior to donation is recommended. Fluconazole-resistant *Candida* spp. or *Aspergillus* spp. are particularly problematic, especially among lung recipients. Dissemination of *Aspergillus* spp. infections must be ruled out.

In certain geographic areas, *Histoplasma*, *Coccidioides*, *Blastomyces* and *Scedosporium* spp. are endemic, and screening may be necessary to rule out active infection in at-risk donors [1, 4, 6, 81-83] (see Table 8.3 and Table 8.8).

Cryptococcus infection may be associated with HIV infections, other immunosuppressive conditions and liver failure.

In persons hospitalised for long periods in the ICU, under anti-microbial therapy and invasive procedures, the risk of colonisation or infection by *Candida* spp. increases. *Candida auris* is an emerging, often multidrug-resistant pathogen with important public health implications. Infections are associated with high mortality, and prevention of transmission requires stringent infection-control measures, making *Candida auris* a potential barrier to donation. One single case of donor-derived *Candida auris* transmission in a lung transplant recipient has been reported [84]. In persons receiving immunosuppressive therapies, there is increased risk of colonisation or infection by opportunistic pathogens, e.g. *Aspergillus* spp. or *Pneumocystis jirovecii* (*carinii*) [81-85]. Another substantial risk factor for acquiring fungal infections is renovation work in the home or hospital. Unfortunately, fungal infections are becoming less and less geographically restricted [86].

In multi-abdominal organ donation, contamination of preservation solution before implantation by various *Candida* spp. has been well described [86]. In such cases fatal complications may occur [87-89].

The reported rate of fungal infections transmitted by organs is low, with the exception of the lungs, although under-detection or under-reporting may occur. In countries with limited medical resources, fungal infections represent a big problem in transplantation procedures.

Disseminated fungal infections must be eradicated before any organ is considered for use. In the case

of lung donations, pulmonary fungal infection/contamination represents a particular problem that must be investigated and properly treated. Proven *Pneumocystis jirovecii* infection of the donor is a contraindication for the use of the lungs.

8.6. Viral infections

8.6.1. Basic screening for viral infections in organ donors

The basic screening for viral infections in deceased organ donors must include at least the serologic tests recommended in section 8.2.

8.6.2. Specific viral infections

For each pathogen discussed in the following sections, the reader is advised to refer to the websites of the organisations mentioned at the end of section 8.2, where the most current epidemiological information can be obtained.

Some viral infections are arthropod-borne and are transmitted by different vectors, e.g. mosquitoes or ticks. The ECDC provides helpful surveillance information on the spread of these vectors in Europe and disease activity in humans [90]. Risk of exposure to various geographically restricted pathogens is based on donor travel and residence history.

For pathogens not listed below, please check Table 8.8 (see §8.11).

8.6.2.1. *Chikungunya virus*

Chikungunya virus (also known as CHIKV; RNA-virus of the *Togaviridae* family) infection is imported from endemic areas; currently these correspond to tropical Africa, parts of Asia, Central and South America, islands in the Indian Ocean, Western and South Pacific and the Caribbean. Up-to-date information about affected areas needs to be checked, due to possible changes in epidemiology. Transmission occurs by bites of infected *Aedes* species mosquitoes (*aegypti* or *albopictus*), which are diurnal (day-active). If competent mosquito vectors are present, imported cases can trigger an outbreak of locally transmitted chikungunya infection, as in northern Italy in 2007 and 2017 and in France in 2010, 2014 and 2017. Since *Aedes albopictus* mosquitoes without infection have been detected all over temperate European regions, it is important to monitor whether they will become infected through movement of infected humans or through importation of infected mosquitoes by international transport. *Aedes aegypti* has recently been re-established in Madeira and around the Black Sea in southern Russia, Abkhazia and Georgia. In 2011, 55 cases of chikungunya fever were reported by 22 European Union (EU) and European Economic Area (EEA) countries; in 2018 and 2019 no autochthonous cases of chikungunya virus disease were reported in EU/EEA member states, but travel-related cases [44]. Infection may manifest through fever, arthralgia or exanthema and rarely as meningoencephalitis, uveitis, retinitis, myocarditis, hepatitis, nephritis, haemorrhage, myelitis or Guillain–Barré syndrome.

Viraemia exists approximately 4 days to 3 weeks after the mosquito bite, during which time transmission by organs can occur. Detection of viraemia by NAT is possible.

Chikungunya infection in solid-organ transplant recipients has rarely been reported but clinical disease does not appear to be more severe in transplant recipients [91-93]. To date, no donor-derived transmission from any SoHO type has been reported. Based on current epidemiologic data, the minimum recommendation is to rule out acute infection in donors living or coming from regions with ongoing outbreaks based on NAT test or clinical suspicion; donors with positive test or clinical symptoms compatible with Chikungunya should be rule out for 28 days from the positive test of the onset of symptoms. These recommendations apply to both living and deceased donors. Organs from these donors might be used before the results of the tests are available. However, in this case, it is recommended to perform a close monitoring of the recipients of organs from donors with documented infection in order to identify future risks due to this emerging pathogen.

Organs from donors viraemic for chikungunya virus should not be used without consulting a transplant infectious disease expert.

8.6.2.2. *Dengue virus*

Dengue virus (DENV: RNA-virus, *Flaviviridae* family) is transmitted by mosquito bites of various *Aedes* species (*aegypti* or *albopictus*). Distribution of *Aedes aegypti* or *Aedes albopictus* without infection in the European region is described in section 8.6.2.1. It is important to monitor whether these *Aedes* spp. in Europe are becoming infected by blood meals on infected humans who migrate by international transport from areas that are affected by infected mosquitoes, in order to identify new risks.

Imported cases of dengue fever in travellers returning from endemic countries are frequently reported. Sporadic locally transmitted cases have been recorded recently in areas of France and Croatia where *Aedes albopictus* is present. In 2012-13, a dengue outbreak involving *Aedes aegypti* transmission was reported in Madeira [94]. More recently, transmission

of dengue has been reported by Croatia, Spain and France [95]. Although environmental conditions are favourable throughout the summer season to support local outbreaks in areas where the vector is present in Europe, a low risk of autochthonous transmission in the EU/EEA is assumed until July 2020 [44].

Infection may be asymptomatic or may manifest as febrile disease, haemorrhagic fever or shock syndrome due to variable immunological response, endothelial failure and vasculitis. After 3-7 days of incubation, viraemia persists for up to 21 days with a risk of transmission through blood or organs. NAT or NS1-antigen-test can confirm viraemia [96].

Transmission of dengue via organ transplantation has rarely been reported [97-100]. Given the limited number of transmissions, biology of dengue transmission via this mode is unknown. Further data are needed to assess the effect of dengue virus on graft function and the effect of immunosuppression on the presentation of dengue.

Based on current epidemiologic data, the recommendation is to rule out acute infection in donors living in or coming from regions with ongoing outbreaks, based on NAT test or clinical suspicion; donors with a positive test or clinical symptoms compatible with dengue should be ruled out for 28 days from the positive test or the onset of symptoms. These recommendations apply to both living and deceased donors. Organs from these donors might be used before the results of the tests are available. It is recommended to monitor recipients of organs from donors with documented dengue infection in order to identify future risks due to this emerging pathogen.

Organs from donors viraemic for dengue virus should not be used without consulting a transplant infectious disease expert.

8.6.2.3. *West Nile virus*

West Nile virus (WNV: RNA-virus) is a member of the *Flavivirus* genus and belongs to the Japanese encephalitis antigenic complex of the family *Flaviviridae*, which includes Japanese encephalitis virus and Usutu virus. It is one example of an arbovirus causing sporadic cases and seasonal outbreaks of neuro-invasive disease (e.g. meningitis, encephalitis, acute flaccid paralysis), combined with febrile illness. Infection is asymptomatic in up to 80 % of cases.

WNV is transmitted through bites of infected mosquitoes (*Culex sp.*), so the risk of infection transmission correlates with the season with the highest probability of mosquito bites, i.e. whole year in southern Europe or late summer/early autumn in the rest of Europe. In summary of the seasonal autochthonous outbreaks in humans and animals during the past decade, WNV is becoming established in the following European regions [44]: south-eastern EU/EAA member states, with spread into Romania, Hungary, Austria, Czech Republic and eastern Germany, as well as Italy and spots in Spain and France [44]. It is advised to check the most recent epidemiological data, as this statement could be outdated beyond July 2020. Since WNV has been a recurrent seasonal problem in some areas of Italy in recent years [101-102], principles in the management of deceased donors may be used according to best practice in Italy. Whenever locally increased rates of WNV infections are detected, either in humans or animals, it is appropriate to consider screening since many cases of transmission occur from donors without febrile neuro-invasive illness.

Viraemia may be detected by NAT, and fatal transmission to organ recipients has been described when WNV NAT-reactive and NAT-negative donors have been utilised [102-105]. Transmissible WNV may be present in potential donors in the absence of positive serology or NAT [104]. There is some evidence that WNV viral nucleic acids and infectious virus remain associated with blood cells after the clearance of virus from plasma [106]. Viraemia may persist after incubation for 2-4 weeks or exceptionally for a few months [107-109]. Detection of antibodies confirms an antecedent infection, but does not clearly identify the risk of transmission through transplantation. Furthermore, positive serology may result from cross-reacting antibodies from other prior flavivirus infections in the donor.

Some data are available on the urinary excretion of WNV following neuro-invasive disease but this issue is completely unexplored in the case of asymptomatic or mild infections. The kidney is a well-established site of active WNV replication in animals [110]. WNV shedding in urine has been reported in humans, not only early post-infection [111], but even years later [112]. Because of longer shedding and higher viral load, urine samples may be more appropriate than blood for WNV testing in blood and organ donors [113]. It was thought that urine might become a specimen of choice to identify WNV in asymptomatic carriers, but an unpublished study of the US-CDC failed to confirm these results [114].

As with other closely related flaviviruses, serological cross-reactivity within the Japanese encephalitis complex is known to occur and results must always be interpreted with caution. Genetic similarity has also led to cross-reactivity especially between WNV and Usutu virus in NAT assays, as ev-

idenced by the case reported from Germany in 2016 [115]. WNV NAT-reactive donors should therefore undergo virus-specific confirmatory tests to determine the actual *Flavivirus* present [116].

Based on current epidemiologic data, the recommendation is to rule out acute infection in donors living or coming from regions with ongoing outbreaks in humans (e.g. using NAT; consider limitations of screening outlined above). Organs from these donors might be used before the results of the tests are available. However, in this case, it is recommended to perform monitoring of recipients of organs from donors with documented infection in order to identify future risks due to this emerging pathogen.

Organs from donors viraemic for WNV should not be used without consulting a transplant infectious disease expert.

8.6.2.4. *Zika virus*

The Zika virus (ZIKV; RNA-virus, *Flaviviridae* family) is transmitted mostly by *Aedes aegypti* mosquitoes. However, *Aedes albopictus* may also transmit the virus and local transmission could occur in continental Europe during the summer wherever *Aedes albopictus* is present. Mild illness (e.g. fever, rash, arthralgia or conjunctivitis) with more than 80 % asymptomatic infections may be observed after an incubation period of up to a week, with symptoms resolving after one week where viraemia may be detected by NAT. In the genito-urinary tract the virus may persist for a longer period.

ZIKV infection during pregnancy is linked to fetal infection and congenital Zika Syndrome. ZIKV infection is also associated with other neurological presentations such as Guillain–Barré syndrome (GBS). The whole spectrum of disease caused by ZIKV remains to be elucidated, but haematological abnormalities such as thrombocytopaenia seem to be one of the findings.

Outbreaks of primary infection are possible in regions with the presence of competent vectors, permissive climate and intense movement of people. This may explain the emerging endemic character of the ZIKV infection (even into temperate regions globally).

Few data exist regarding the clinical characteristics of ZIKV infection in immunocompromised hosts. Laboratory screening protocols for transplantation, to differentiate ZIKV infections from other endemic viral diseases and for the detection of possible donor-derived infection, have not been stated. The diagnosis of ZIKV infection remains a challenge, fuelled by the lack of standardised commercially available diagnostic tests and validated reference diagnostic laboratories, as well as the limited duration of ZIKV viraemia [117]. *Flavivirus* serology is complex, as a high degree of cross-reactivity is seen among closely related viruses; in the case of ZIKV, separation between ZIKV and dengue virus immune responses is very difficult. Therefore, serological screening may not be helpful in donor characterisation.

The first case series of ZIKV infection in solid-organ recipients, with a description of clinical and laboratory features and therapeutic management, has been recently published [118]. This report did not demonstrate more severe disease in transplant recipients. A probable case of transfusion-transmitted ZIKV infection in a liver transplant recipient was published in 2016 with no indication of a more severe course of infection [119]. The risk of transmission by solid-organ transplantation at the date of publication of this Guide is currently unknown, but it is theoretically possible.

Since *Aedes* species as vector may transmit other viruses too, e.g. dengue or chikungunya viruses, considerations about ZIKV overlap with concepts of how to minimise the risks associated with possible infection by these viruses. In cases of travel to, or living in, Zika-endemic areas 28 days prior to donation in symptomatic donors, targeted NAT screening may be helpful to identify the correct pathogen. In asymptomatic deceased donors, the risk of donor-derived infection should be balanced with the benefits of transplant in each potential recipient. In living donation during pre-donation counselling, the risks can be discussed with the donor and recipient for proper timing of the procedure.

Based on current epidemiologic data, the recommendation is to rule out acute infection in donors living in, or coming from, regions with ongoing outbreaks based on NAT test or clinical suspicion; donors with positive test or clinical symptoms compatible with Zika should be ruled out for 28 days from the positive test of the onset of symptoms. These recommendations apply to both living and deceased donors; organs from these donors might be used before the results of the tests are available. However, in this case, it is recommended to monitor the recipients of organs from donors with documented infection according to updated protocols, in order to identify future risks due to this emerging pathogen.

Organs from donors viraemic for Zika virus should not be used without consulting a transplant infectious disease expert.

8.6.2.5. *Yellow fever virus*

Yellow fever (YF) is an African mosquito-borne infection of primates. It is caused by a virus of the *Flavivirus* genus of the *Flaviviridae* family. In its natural habitat, it is transmitted between monkeys by forest-dwelling primatophilic *Aedes* mosquitoes. Through the slave trade, the virus and its vectors (*Haemagogus, Sabethes* and *Aedes aegypti*) were introduced to the Americas, where the virus is also enzootic in forest habitat. Sylvatic infection of humans occurs when they enter the forest to hunt, gather food, harvest timber and so on. Forest-infected persons can initiate human-to-vector-to-human transmission if suitable peridomestic vectors are present in towns and villages. In the urban environment, *Aedes (Stegomyia) aegypti* (Linn.), a forest species that has adopted the human domestic environment, is a highly effective vector for yellow fever virus (YFV). This mosquito is also the principal urban vector of dengue and chikungunya viruses.

YF is distributed in west, central and east Africa and in South America, from Panama to the northern part of Argentina. It has never been detected in Asia. Catastrophic epidemics, with tens of thousands of deaths, have been recorded in rural Africa. The vector *Aedes aegypti* was once endemic in Europe, and responsible for large epidemics of YF and dengue. The reason for its disappearance after the Second World War has never been explained. It is still present in the United States and has been recorded in 21 states. It is conceivable that the vector could become re-established and widespread in Europe, as has happened in recent years with another putative vector, *Aedes albopictus*.

In Brazil, since the end of 2016 a significant increase in the number of YF cases has been observed in highly populated areas previously not affected by YF, affecting monkeys living in parks and woods near urban areas. YF has never previously been reported in transplant recipients. The first reported case of yellow fever in a kidney transplant recipient in Brazil and the re-emergence of arboviruses in many areas of the world dictate the need of studies aimed to answer multiple unanswered questions [120-121].

There are no specific criteria for the deferral of a prospective donor with a history of YF. Therefore, it is suggested that the same general recommendation, applied in cases of non-specific acute viral illnesses, be applied in these cases: donors must have recovered, be afebrile and asymptomatic on the day of donation and may donate 28 days after full recovery, based on clinical observation, e.g. [122-123]. Deferral of living donors returning from areas affected by malaria will be sufficient to prevent YF infectious donations: precautionary deferral is suggested for 28 days in the case of non-vaccinated living donors returning from an area affected by YF but non-endemic for malaria. In deceased donation, a case-by-case decision after consultation of a transplant infectious disease expert is required.

If an organ donor has received YF vaccine during the four weeks before donation, an individual risk assessment of the immune status of all prospective recipients is mandatory. There are two possible and one probable transfusion-related transmissions of YF vaccine virus from a donor who had received a YF vaccination 4 days before the donation [124]. YF vaccination is contraindicated for immunocompromised patients after solid-organ and haematopoietic stem-cell transplantation because it is a live attenuated preparation. Potential transplant patients living in countries endemic for YF or planning travel to endemic countries in the future should be immunised before transplantation [125].

8.6.2.6. *Cytomegalovirus*

Between 20 % and 100 % of the adult population (increasing with age) in Europe are latently infected with *Cytomegalovirus* (CMV: DNA virus, *Herpesviridae* family), with significant geographic variation. Following primary infection, most immunocompetent individuals remain asymptomatic. No contraindications exist for organ donation in the case of a donor with latent CMV infection [6].

De novo infection by a graft in naïve recipients, as well as reactivation of a latent infection in the recipient should be avoided by specific anti-viral prophylaxis or virological monitoring and pre-emptive therapy. Most CMV-active anti-viral agents are, at least partially, effective in preventing/treating other herpes viruses – including *Herpes simplex* virus (HSV) and varicella–zoster virus (VZV) – but not all, e.g. letermovir. Recipient morbidity increases in the case of donor-seropositive and recipient-seronegative (D+/R–) combinations. Consensus guidelines for prevention and treatment of CMV infection in solid organ transplant recipients were published in 2018-19 by the Transplantation Society and the American Society of Transplantation [126-127].

Organs can be accepted regardless of the anti-CMV IgG status of the donor. Suitable prophylaxis or virological monitoring with pre-emptive treatment should be adopted in recipients, particularly in donor-positive/recipient-negative (D+/R–) cases.

8.6.2.7. *Epstein–Barr virus*

In Europe, more than 90 % of all adults are infected with Epstein–Barr virus (EBV: DNA virus, *Herpesviridae* family). After primary infection with or without disease, people may remain asymptomatic if not immunocompromised.

EBV transmission to immunologically naïve transplant recipients increases the risk of post-transplant lympho-proliferative disorders (PTLD). This risk requires regular follow-up of all transplant recipients and consideration of specific therapies if viraemia or malignancy is identified.

In the case of EBV D+/R– (for instance, most paediatric transplant recipients), protocols for close monitoring of such recipients contribute to reducing the fatal complications of PTLD by earlier diagnosis. It should be noted that there is no prophylactic treatment which can prevent primary EBV infection. Still EBV-DNA monitoring and early management should be considered for all D+/R– recipients. Reduction of immunosuppression is the preferred pre-emptive intervention for EBV DNAemia. Anti-viral therapy as a sole pre-emptive intervention is not recommended [128]. Adoptive immunotherapy, using either *in vitro* expanded autologous or HLA-matched banked third-party donor polyclonal EBV-specific cytotoxic T-lymphocytes, has also been used for PTLD prevention, given either to all high-risk patients or pre-emptively in response to EBV DNAemia. This prevention approach has been most extensively evaluated in haematopoietic stem-cell transplant recipients and is currently most commonly used when rituximab pre-emption fails; data in solid organ transplant recipients is limited. Access, cost and lack of definitive evidence of effectiveness in the solid organ transplant population prohibits widespread implementation of this approach [129-130].

In cases of suspected acute mononucleosis, EBV infection can be ruled out by an investigation of the presence of EBV-DNA and anti-EA in peripheral blood.

Organs can be accepted regardless of the anti-EBV IgG status of the donor. Proper follow-up and/or surveillance for PTLD is required, particularly in children and D+/R– cases.

8.6.2.8. *Kaposi sarcoma-associated herpes virus or human herpes virus 8*

Kaposi sarcoma-associated herpes virus (KSHV) is a double-stranded DNA herpes virus belonging to the gamma *Herpesviridae* subfamily; the other human herpes virus in this group is the Epstein–Barr virus. Human herpes virus 8 (HHV8) has been associated with the development of three neoplastic diseases: Kaposi sarcoma, primary effusion lymphoma and multicentric Castleman disease. As is the case with all herpes viruses, the KSHV life-cycle includes both latent and lytic phases.

Unlike most herpes viruses, human infection with KSHV is not ubiquitous. Sero-prevalence is estimated to be between 0 % and 5 % in North America, northern Europe and Asia; between 5 % and 20 % in the Mediterranean and Middle East; and > 50 % in some parts of Africa.

Transmission of KSHV from organ donor to recipient has been documented through assessment of sero status before and after transplant and by molecular epidemiologic studies [131-142]. In immunocompromised persons, fever, splenomegaly, lymphoid hyperplasia, pancytopaenia and occasionally rapid-onset Kaposi sarcoma have all been described in association with apparent primary KSHV infection [136, 138-141, 143]. However, in immunocompromised transplant recipients, KSHV is more often associated with neoplastic diseases. Early identification of primary or reactivated infection offers the possibility of careful alteration of immunosuppression, where appropriate, or pre-emptive anti-viral treatment; this is associated with more favourable outcomes when compared to late diagnosis of symptomatic disease.

Various assay formats have been developed to detect antibodies against latent and lytic proteins: immunofluorescence, Western blot and ELISAs. Some of these assays have been used for sero-epidemiologic studies, but there are limitations to their usefulness in clinical daily practice, such as the lack of standardised methodologies and international controls. Moreover, the sensitivity of serological assays is variable and ranges from approximately 80 % to greater than 90 %. The optimal serologic assay technique cannot be determined at present, with few commercially available tests and several assays developed in house. It has been suggested that a combination of whole virion ELISA and lytic immunofluorescence assay may be the most sensitive and specific serological method for diagnosing KSHV infection.

HHV8 serology is generally unavailable prior to deceased donor organ transplantation, and a donor screening policy may be adopted almost exclusively for living donors. Many studies have suggested the potential utility of the screening of KSHV antibodies among organ donors and recipients. These studies have argued in favour of KSHV screening, sometimes even in low-KSHV infection-prevalence countries. Organs should not be excluded but information on the KSHV status provides the opportunity to monitor, clinically and biologically, patients at risk

for KSHV-related disease development. Therefore, targeted antibody screening according to risk could be done in the days following transplantation, with the results transmitted retrospectively to physicians.

Universal screening of donors for KSHV is generally not necessary. However, since donor-derived primary KSHV infection may be associated with severe disease, screening of donors for KSHV anti-lytic and anti-latent antibodies is recommended for donors and recipients coming from areas with high prevalence. In cases of D+/R– mismatch, close monitoring of the recipient for KSHV-DNA in blood is recommended in order to identify infection early.

8.6.2.9. *Herpes simplex and varicella–zoster viruses*

No contraindication to organ donation exists for donors presenting with only latent *Herpes*-family viral infections [6]. No specific donor screening is required [6]. However, it is important to be aware of fatal *de novo* infections in naïve recipients by grafts procured from latently infected donors, as well as reactivation in latently infected recipients [144-148]. In this context, the sero status of the recipient is much more informative in terms of risk assessment and management.

Primary infection from the allograft (donor-derived infection) has been described in liver, kidney and other organ transplant types and can be quite severe; in the absence of any intervention, primary HSV infection in the early post-transplant period is very often fatal. Some transplant centres perform retrospective, additional donor tests for HSV or VZV antibodies in cases of sero-negative recipients in order to decide on specific anti-viral prophylaxis or treatments and follow-up. Only a few case reports [149-152] exist; therefore HSV-specific prophylaxis should be considered for all HSV-1 and HSV-2 sero-negative recipients who are receiving organs from seropositive donors but who are not receiving anti-viral medication for CMV prevention that has activity against HSV. Note that universal donor screening is not recommended, based on the known high seroprevalence in Europe.

Donors with successfully treated *Herpes encephalitis* infection can be used with some precautions, particularly if the recipient is HSV seronegative (e.g. avoid D+/R– combination, for which see §8.13).

Organs can be accepted from donors with latent α-herpes-family viral infections, but not in the case of acute Herpes viraemia in the donor without effective anti-viral treatment. Therefore HSV-specific prophylaxis should be considered for all HSV-1 and HSV-2 seronegative recipients who are receiving organs from seropositive donors but who are not receiving anti-viral medication for CMV prevention that has activity against HSV.

8.6.2.10. *Hepatitis A virus*

Hepatitis A virus (HAV: RNA-virus, *Picornaviridae* family) infection is not a risk for transplantation unless in cases of acute infection in the donor. A case of donor-derived transmission through pancreas and intestinal transplantation has been described [153], but notice that the donor was retrospectively found to be viraemic with HAV and the paediatric recipient had very prolonged viraemia and faecal shedding, with diagnosis made due to transmission to two healthcare workers. Recovery from HAV infection or prophylactic vaccination status is indicated by anti-HAV-IgG reactivity. In 2012/13, a HAV outbreak in EU member states, linked to frozen berries, was responsible for an increased number of cases [154].

Since February 2016, growing numbers of confirmed hepatitis A cases infected with three distinct strains of sub-genotype IA virus have been reported in EU countries. Most cases are reported among adult men who have sex with men (MSM), with only nine women affected [155]. As of June 2017, at least 16 EU member states had reported 1 434 cases infected with one of the three cluster strains. An additional 2 660 cases probably (or suspected to be) associated with this outbreak were reported [156]. In the case of a donor belonging to the above risk population or with suspected acute infection, consulting a transplant infectious disease expert is suggested. Potential recipients should also have been vaccinated against HAV before being put on a waiting list [26].

Organs can be accepted regardless of the anti-HAV IgG status of the donor, except in cases of acute HAV infection in the donor.

8.6.2.11. *Hepatitis B virus*

At least 10 % of the European population, with significant geographic variation, have been in contact with hepatitis B virus (HBV: DNA virus, *Hepadnaviridae* family) [4].

In the case of donors with HBV viraemia (indicated by an HBsAg-reactive result or detectable HBV DNA in the blood), HBV will be transmitted by any organ or tissue. Such infected donor organs may be used in special circumstances, when either the recipient receives HBV prophylaxis by anti-viral therapy in addition to hepatitis B hyperimmunoglobulin (HBIG), or when the recipient is already immune [58, 157-159]. Lifelong monitoring for HBV is necessary. However, a breakthrough HBV infection may occur despite the prophylactic use of anti-virals and HBIG

(especially in liver transplantation). For every HBsAg positive donor, HDV coinfection must be excluded (see §8.6.2.13).

Table 8.5. **Potential risks of organs transplanted from HBV-infected donors**

Hepatitis B tests	Conclusion	Liver: transmission risks to be considered and possible recipients to be selected for transplant	Non-hepatic organs: transmission risks to be considered and possible recipients to be selected for transplant
HBsAg+ Anti-HBc–	HBV viraemia (exceptional case)	HBV transmission occurs: • transplantation of organs in vital cases, HBV-infected recipients or vaccinated recipients with HBV prophylaxis* • may also be used in recipients of other organs with specific consent, prophylaxis and lifelong monitoring*	
HBsAg+ Anti-HBc+	HBV viraemia		
HBsAg– Anti-HBc+	Hepatocyte infected, usually no viraemia	HBV transmission occurs with liver transplant: • transplantation of organs in HBV-infected recipients or vaccinated recipients with HBV prophylaxis*	Transmission unlikely: • transplantation of organs in vaccinated or infected recipients • may also be used in other recipients with (or without) HBV prophylaxis* and with lifelong monitoring

+ = reactive; – = non-reactive

* HBV prophylaxis = anti-viral treatment (and HBIG) as well as lifelong monitoring (serology and NAT) required. In recipients with appropriate own immunological protection against HBV after vaccination, discontinuation of anti-viral treatment can be considered on a case-by-case basis, but evidence is lacking [162-163].

Note: Only in donors with anti-HBc reactivity, anti-HBs might be determined for additional information in case of unreliable anti-HBc tests (unless HBV-NAT of blood and liver tissue is available).

Individuals who have controlled and cleared their natural infection usually become HBsAg non-reactive, anti-HBc reactive and anti-HBs reactive (> 10 IU/L). Except for the liver, the use of organs from such individuals rarely results in transmission of HBV [157, 160-161]. However, grafts from such donors should preferably be used in recipients with current or previous HBV infection or successful vaccination. Lifelong monitoring is recommended [159]. Except for the liver, organs may also be used in HBV-naïve recipients after informed consent and when combined with special monitoring of the recipient, including HBV-NAT and HBsAg screening at least during the first year after transplantation [162]. In recipients of non-hepatic grafts HBV prophylaxis with anti-viral agents may be considered but it is most likely unnecessary.

In anti-HBc reactive donors (with non-reactive HBsAg and irrespective of anti-HBs titres), the hepatocytes remain latently infected with the virus – by viral covalently closed circular DNA (cccDNA) located in the nucleus and/or viral DNA integrated in the genome of the hepatocyte – and reactivation of latent infection can occur in the setting of immunosuppression, especially in such liver-graft recipients. In such cases, in liver recipients without initial protection against HBV, lifelong treatment with HBV-specific anti-viral therapies will be required [163]. Such infected liver grafts may also be transplanted into recipients who have their own immunological control of HBV infection through previous vaccination or infection. Most transplant centres use HBV-specific anti-viral agents in recipients with previous HBV infection and virus replication [163]. Any recipients of HBsAg-reactive or anti-HBc reactive donor livers should be monitored throughout life [163] for HBV reactivation or rare breakout due to mutation of HBV acquired from the donor via the graft. HBV vaccination does not always prevent this due to escape mutants [164]. The epidemiology of HBV mutants is not well studied in all European countries, but there must be awareness of the different HBV variants that can pose difficulties in HBsAg screening. Moreover, HBIG prophylaxis or previous immunity in the recipient will be ineffective against escape mutant strains.

The clinical relevance of isolated anti-HBc reactivity, without reactivity of any other HBV serological marker, is uncertain [165]. This is suggestive of prior, long past, HBV infection in the donor with undetectable anti-HBs and anti-HBe, false positive serological reactivity or passively acquired anti-HBc.

In the case of an anti-HBc reactive donor, only negative HBV-NAT from liver tissue would exclude HBV infection. This could be done as a complementary investigation after transplantation. Unfortunately, such measurements are not yet standardised. Thus, further recommendations cannot be provided at this stage.

HBV infection with HBV pre-core mutants is frequent (> 60 %) in some areas of Europe [166]. These mutants lack the genetic information for the production of HBeAg. Therefore, determination of HBeAg or anti-HBe is of limited informative value. After transplantation of organs from donors with isolated

anti-HBc reactivity, seroconversion to anti-HBc has been documented in recipients. Furthermore, HBV escape mutants occur (despite anti-HBs prophylactic treatment); these donors are usually HBsAg negative, anti-HBs and anti-HBc reactive and HBV DNA reactive [167-169].

It should be considered whether, depending on the prevalence of HBV mutants, testing algorithms might miss HBsAg reactivity in some populations – also depending on the country where infection occurred. Hence, laboratories should select appropriate testing platforms.

In the case of a donor with known HBV infection, it will be helpful to provide recipient centres with all known data, similar to the form suggested for HCV (see §8.6.2.12). Then, even a liver graft from a HBsAg-reactive donor may be used with proper safety precautions [170]. Still HDV co-infection must be excluded (see §8.6.2.13).

In every donor, HBsAg and anti-HBc must be determined. In any case of a reactive result for HBsAg or anti-HBc, follow the algorithm in Figure 8.4 in order to provide all information needed. Table 8.5 summarises the potential risks of organs used for transplantation from HBV-infected donors according to their screening results.

8.6.2.12. *Hepatitis C virus*

Hepatitis C virus (HCV: RNA-virus, *Flaviviridae* family) infection is transmitted by any donor with an HCV-NAT reactive test result, irrespective of antibody status. In donors with anti-HCV reactive results and viraemia ruled out definitively by HCV-NAT this may not occur [171], with a remaining risk due to occult HCV infection or inappropriate sensitivity of the HCV-NAT test. Potentially, about 0.5-18.5 % of all donors are HCV-infected globally, with extensive variation according to geographic prevalence and occurrence of risk behaviours, e.g. intravenous drug abuse, intra-nasal cocaine sniffing, medical procedures [44, 172].

Although viral load may fluctuate in chronically HCV-infected individuals, it generally remains above 1 000 IU/mL. Still the detection level of the NAT test used should be < 15 IU/mL. The fluctuation of viral load can also be caused by acute reinfection of people who were able to clear previous infection spontaneously [173].

Spontaneous clearance of viraemia can occur in up to 25 % of the people with acute HCV infection. Which factors enhance or restrict this chance of clearance is a matter of extensive research. Due to improvements in HCV treatment, more people will achieve a sustained virological response with no viraemia detectable by HCV-NAT after therapy, regardless of the HCV genotype. The issue of potential HCV-persistence in such patients with sustained virological response is controversial and unresolved, with no evidence of transmission in such circumstances.

Organs from donors with HCV viraemia should only be transplanted into recipients with HCV viraemia or recipients with an otherwise life-threatening condition, since HCV transmission is very likely, or into recipients receiving pre-emptive/post-exposure treatment definitively within an approved study protocol until appropriate evidence is available [174-175]. In the case of donors with anti-HCV reactive results and viraemia ruled out definitively by HCV-NAT due to sustained virological response after effective treatment or spontaneous clearance after acute infection, transmission is unlikely to occur [171], but is possible e.g. by liver grafts [176]. Such grafts can be used in recipients willing to accept the risk after informed consent and compliance with follow-up by HCV-NAT screening, and HCV-therapy if infection occurs.

Whatever the benefits of knowing the donor HCV genotype (and/or viral load) may be, logistics preclude its determination at the time of organ donation. In addition, mixed HCV infection has not been associated with increased mortality [177-178]. One study has reported that, in recipients where the donor viral strain predominated, HCV recurrence was less frequent than in cases where the recipient viral strain was predominant [179-180]. With the currently available pan-genotypic DAAs, the issue of the genotype is less relevant [181]. It might be useful for better understanding of the prevalent genotype in the recipients, but it has no impact on the post-transplant treatment because pan-genotypic DAAs are recommended as therapy in patients after transplantation according to the guidelines of the European Association for the Study of the Liver [174, 182] (see Appendix 16).

NAT testing of recipients should be used post-transplant to detect donor-derived HCV transmission [27] because most patients with donor-derived HCV fail to develop serologic evidence of infection despite persistent high-level viral replication. Testing should be done optimally within the first month post-transplant to allow early initiation of DAA.

The new DAAs against HCV provide an opportunity for reassessment of organ transplantation from HCV-positive donors (nonviraemic as well as viraemic) to HCV-negative recipients [32-34, 36-40, 183-193]. In fact, the results of clinical trials to assess the safety of this approach in kidney, liver and thoracic organ transplantation have been published

[34-40, 184-186]. Current guidelines recommend that such HCV D+/R– transplants take place in a research setting until all of the challenges associated with this type of transplant are understood [31, 174-175]. Furthermore, all previous conclusions about the risks associated with transplantation of grafts procured from expanded-criteria donors into HCV-infected recipients must be revised since effective treatment of HCV infection is possible and this should not be withheld for such recipients. In addition, due to the current availability of pan-genotypic DAA, the issue of genotyping at the time of organ procurement becomes much less relevant.

The available DAA drugs for interferon-free anti-viral treatment should be applied according to the established guidelines [174-175, 181-182] (see Appendix 16). When using grafts from HCV-viraemic donors, a pan-genotypic regimen will have to be applied within the pre-emptive therapy of *de novo* HCV-exposure. In end-stage renal disease patients, impaired renal function (e.g. eGFR < 30/mL/min/1.73 m^2) might raise the question whether to treat the recipient before or after transplantation of allografts from HCV-viraemic donors in case of assumed short waiting times. Since waiting times are unpredictable (e.g. due to HLA immunisation) and DAAs will be available for use in patients with impaired renal function, preference can be given to early eradication of HCV to avoid further complications.

In every donor, anti-HCV must be determined:

1 In cases of reactive results, follow the algorithm in Figure 8.3.

2 In cases of anti-HCV reactive results, HCV-NAT should be performed to assess whether viraemia clearance exists or not (spontaneous or due to sustained virological response after therapy).

Table 8.6 summarises the potential risks of organs used for transplantation from HCV-infected donors according to their screening results.

For the appropriate selection of transplant recipients, it is helpful to obtain the following information in a donor with a HCV infection:

a. Has there been previous HCV infection?

b. Was any HCV treatment given before?

i. If yes: what kind of medication was used? What kind of virologic response was achieved or did resistance develop? How was effective treatment monitored and what were the results of NAT (qualitative)? Was the genotype determined? Was the therapy complied with throughout its duration?

ii. If no: what was the reason for not treating the infection?

c. Is there any information about the source of infection?

d. Transplant centres that transplant organs from HCV-positive donors should develop protocols for obtaining informed consent, testing and treating recipients for HCV, ensuring reimbursement of recipient's treatment with DAA and reporting new infections to public health authorities.

8.6.2.13. *Hepatitis D virus*

Hepatitis D virus (HDV: RNA-virus, the only agent of the genus *Deltaviridae*) infection, as with HBV infection, is mostly an issue for countries with a high prevalence of HDV.

Defective HDV requires the HBsAg for replication. Donor-transmitted HDV infections must be avoided by adequate screening of HBsAg-reactive donors because therapeutic options do not currently exist [194-195] (e.g. HDV-NAT, anti-HDV despite limited availability).

Table 8.6. **Potential risks of organs transplanted from HCV-infected donors**

Hepatitis C tests	Conclusion	Liver: transmission risks to be considered and possible recipients to be selected for transplant	Non-hepatic organs: transmission risks to be considered and possible recipients to be selected for transplant
Anti-HCV+ HCV-NAT not available	HCV viraemia cannot be ruled out*	HCV transmission occurs by the graft: Vital cases or viraemic recipients with mandatory HCV-prophylaxis/pre-emptive treatment, also requiring lifelong monitoring by serology and NAT. In HCV-naïve recipients, grafts from known HCV-viraemic donors should currently only be used in an approved study protocol and/or with informed consent in dire recipient conditions.	
Anti-HCV+ HCV-NAT+	HCV viraemia		
Anti-HCV– HCV-NAT+			
Anti-HCV+ HCV-NAT–	HCV viraemia unlikely*	HCV transmission may not occur; transplantation after informed consent of recipient in study protocol possible for D+/R–. No restrictions for D+/R+.	

+ = reactive; – = non-reactive.

* HCV viraemia may be below the detection threshold of HCV-NAT. This causes a non-reactive result. Therefore, appropriate data should be collected (about the course of HCV treatment or evidence for spontaneous clearance).

Note: prospective HCV-NAT is only recommended for donors with an elevated risk of HCV infection or anti-HCV positive donors.

The therapeutic landscape of HDV therapy is changing rapidly because some promising new compounds, given as monotherapies or in combination with Peg-IFN, are now under investigation in phase I and II clinical trials [196-197]. Short-term administration of the entry inhibitor myrcludex-B (MyrB) has been shown to be safe and effective in phase II studies in patients co-infected with hepatitis B virus (HBV) and hepatitis delta virus (HDV). However, its effectiveness and safety are unknown during long-term and high-dose treatment [198-199]. The availability of new anti-viral agents with activity against HDV might allow in the future a more liberal use of HBV/HDV co-infected donors.

Organs from donors with HDV infection are usually not accepted because we still lack effective treatment for HDV. Organs from HBsAg+ with HDV co-infection can be used only in HBsAg+, HDV-RNA+ recipients.

8.6.2.14. *Hepatitis E virus*

Currently, the impact of Hepatitis E virus (HEV: RNA-virus, *Hepeviridae* family) infection in solid-organ transplant recipients cannot be well assessed because of the variable endemic occurrence in European organ or blood donor populations.

At least four genotypes cause infections in humans (HEV-1 to 4). HEV-1 and HEV-2 infect only humans, transmission is mainly oral-faecal, occurring in tropical endemic areas and causing acute, self-limited illness apart from infections in pregnancy when morbidity is significantly increased; materno-fetal transmission has been described and no chronic infection has been reported with these types. However, HEV-3 and HEV-4 have animal reservoirs and are responsible for autochthonous cases in industrialised countries. The main source of zoonotic HEV transmission is the consumption of raw or undercooked, infected pork and game meat or direct contact with infected animals; transmission via blood components has also been documented. Genotype 3 is prevalent in some EU member states, where it causes mostly asymptomatic and sometimes symptomatic, self-limited infection. HEV-3 is known to cause persistent infection in immunocompromised individuals and (in particular) in recipients of solid organs, where it appears to be linked to progression to cirrhosis [200-201].

The pathogenesis of hepatitis E is still poorly understood. Negative strands of HEV RNA, indicating virus replication, have been detected in the small intestine, lymph nodes, colon and liver of pigs, indicating extra-hepatic HEV replication [202]. HEV then replicates in the cytoplasm of hepatocytes and is released into both blood and bile. The liver damage induced by HEV infection may be immune-mediated by cytotoxic T-cells and natural killer cells since HEV is not cytopathic. HEV first infects the intestinal tract (with excretion via faeces) and then the blood and the liver (with excretion via bile). After an immunological response, HEV is cleared from the blood and, after a maximum of 120 days, from the intestine. Chronic HEV infection (by HEV-3) is usually observed in patients with profound immunosuppression.

HEV infection has been observed in liver, lung, kidney, haematopoietic stem cell, heart and simultaneous kidney–pancreas recipients. Reactivation of HEV infection has been reported without association to the donor [203]. Donor-derived transmissions have been reported for various organs from countries with predominating HEV genotype 3, e.g. [204-206]. Hereby donors can be asymptomatic.

In contrast, in recipients mild elevation of liver enzymes, signs of rejection and other complications may mimic ongoing HEV infection with viraemia. Without treatment this ends up in rapid progression to liver fibrosis. The commonest route of infection is dietary, even in the transplant recipient. Depending on the local epidemiology, transplant centres must have protocols for HEV testing recipients. As a minimum, HEV must be excluded in the presence of any alteration of liver function test results in a recipient, but chronic infection in recipients without abnormalities is known. Therefore, recipients should be monitored by HEV-NAT regularly. Treatment of choice of infection is cautious modulation of immunosuppression and oral Ribavirin, which is efficient in controlling HEV replication. Ribavirin is the drug of choice and seems to be effective in immunosuppressed recipients [207-209].

In cases of acute infection in the donor with viraemia, organs should not be transplanted without proper risk–benefit assessment and application of pre-emptive therapy protocol. After recovery from HEV infection, organs can be transplanted. In HEV-endemic countries, retrospective screening of donors by HEV-NAT should be considered for further management of recipients [41, 47]. In non-endemic countries this is currently a point of discussion.

Organs can be accepted regardless of the anti-HEV-IgG status of the donor, except in cases of acute HEV infection in the donor with known viraemia, where consultation of a transplant infectious disease expert is recommended.

In HEV-endemic countries, retrospective screening of donors by HEV-NAT should be considered. In cases of HEV-viraemic donors, the treatment option with ribavirin should be taken into consideration. However, some recipients (especially kidney-transplanted patients) may have viral rebounds even after an aviraemic interval. In such cases, continuous monitoring of HEV RNA is recommended.

8.6.2.15. *Human immunodeficiency virus*

Organs from donors with HIV (RNA-virus, *Retroviridae* family) infections have so far been utilised intentionally only in a limited number of cases. This includes the experimental protocol for HIV-infected recipients in South Africa. The protocol requires strict adherence of the recipient to highly-active anti-retroviral treatment [210]. More recently, liver and kidney transplantation from HIV-positive donor to HIV-positive recipients has been reported in Switzerland [211], UK [212], USA [213], Canada [214] and Italy [215]. Further HIV-infected donors have been inadvertently used after false negative testing, resulting in unintended transmission into previously uninfected recipients [216-217].

With the aim of generating evidence-based, research-driven data to produce criteria that would facilitate the feasibility of HIV-to-HIV transplantation in the United States, the US Congress approved the HIV Organ Policy Equity Act (HOPE) Act (42 U.S.C. §274f-5b) in November 2013, mandating a revision to the 1988 National Organ Transplant Act (NOTA) prohibition of transplanting organs from HIV-positive donors. The US Department of Health and Human Services was charged with developing guidelines for clinical research involving HIV-positive organs and, on 25 November 2015, the final HOPE Act safeguards and research criteria were published [218-219].

Donors who present with evidence of HIV infection or 'HIV-related diseases' should never be used for HIV-uninfected individuals. However, if HIV-RNA is undetectable (under anti-retroviral treatment) and there are no relevant co-infections, organs from HIV-infected donors may be used for HIV-infected recipients within an experimental context with appropriate results [220]. The specifically designed protocol has to be approved and permitted by local regulation and national law. However, anti-HIV-1/2 reactive status in potential donors is still regarded as a contraindication for organ donation in most European countries.

Organ transplantation using organs from HIV-positive donors poses further challenges. In addition to the risk of transmitting opportunistic infections or malignancies, there is the potential risk of HIV superinfection in the recipient, i.e. transmission of HIV strain with resistance to anti-retrovirals that may preclude HIV suppression after transplantation. However, in the UK case, despite the transmission of a different strain, which was responsible for an HIV viral load rebound on day 2 after transplantation, resuppression of the recipient's viral load occurred within the first seven postoperative weeks without a change in the highly-active anti-retroviral treatment (cART regimen). His viral load has subsequently remained undetectable throughout the first five years after transplantation. Note that in some populations the target organs for HIV infection are the kidneys (e.g. HIV-nephropathy in South Africa). Nonetheless, transplantation of HIV-infected patients receiving highly-active anti-retroviral treatment before and after transplantation has demonstrated excellent recipient survival when they were carefully selected and monitored by experts, with particular emphasis on the complex drug–drug interactions between the anti-HIV and anti-rejection medications [221-222].

Although transplantation from HIV-positive to HIV-positive is promising, it remains unclear whether or not patients may be inadvertently harmed. Accordingly, as experience increases, ethical practice will demand measures to ensure that risks are identified and minimised [223].

The serologic HIV test should detect antibodies against HIV-1 and HIV-2, as well as group O of HIV-1. Fourth-generation assays include the test for the p24 Antigen of HIV-1, which acts as a marker of early infection during seroconversion. For increased-risk individuals, NAT is recommended prospectively (see §8.2 and §8.3). Although NAT currently focuses on HIV-1, NAT screening should be extended to HIV-2 for specific populations in HIV-2 endemic areas or European sub-populations with immigrants coming from HIV-2 endemic areas.

Physicians need to be aware of the diagnostic challenges posed by the growing use of HIV post-exposure prophylaxis following sexual exposure, whereby serological responses are modified and viral load measurements are affected. This may need to be considered and taken into account when obtaining donor history, as and when appropriate with the known limitations of obtaining data precisely.

It is probably time to reconsider the possibility of using organs from HIV-infected donors for HIV-uninfected individuals for life-saving procedures, as recently reported from South Africa [224].

Given that HIV is currently easily manageable, and transplant recipients appear to tolerate ART and immunosuppression well, if the immediate benefit outweighed the immediate risk it would be reasonable to consider this opportunity. A further consideration is the possibility of preventing possible HIV transmission by initiating cART prophylaxis in the recipient prior to the procedure, as well as selecting a long-term virally suppressed donor. There are many ethical barriers to overcome before this option becomes a reality but it is worthwhile opening the debate on this issue. An additional question is how to proceed with cases on first-line therapy versus cases with second- or third-line therapy and not well suppressed viral load. Currently this 'reconsideration' can only be discussed within an appropriate clinical trial and it cannot yet be recommended for daily practice in Europe.

Organs from anti-HIV-reactive donors should not be used for HIV-naïve recipients. Such organs may be offered, under careful surveillance, to selected HIV recipients under a specifically designed protocol.

With the currently available anti-retroviral agents for life-saving transplantation, the use of organs from HIV-infected donors would be reasonable if the recipient were treated accordingly within an appropriate study protocol from a scientific point of view.

8.6.2.16. *Human T-lymphotropic virus*

Retrovirus infection by human T-lymphotropic virus-1 (HTLV-1: RNA-virus, *Retroviridae* family) results in insertion of the viral genome into T-lymphocytes. HTLV-1 is transmitted through similar routes to those for HIV. HTLV-1-associated T-cell leukaemia develops in 2-5 % of cases, usually 20-30 years after infection. HTLV-1 may also cause spastic tropical paraparesis (also called HTLV-associated myelopathy or HAM) in 0.25-4 % of cases, with onset of disease following soon after the initial infection. No proven treatment for HTLV-1 infection exists, although chemotherapy may treat associated leukaemia [22].

Human T-lymphotropic virus-2 (HTLV-2) has not been definitively associated with human disease [22].

In Spain, the general prevalence of HTLV-1/2 was reported to be below 1 % and, in blood donors, below 0.1 %. In an unpublished series from Germany in the early 1990s, HTLV prevalence was essentially 0 % in organ donors. In first-time blood donors in Europe it is only in Romania that a higher prevalence of 5.3/10 000 exists [225]. For the Middle East region (Asia) the same must be assumed. However, transmission of HTLV by blood or organs has been reported in a few cases globally.

Unfortunately, current screening methods cannot differentiate between HTLV-1 and HTLV-2 infections. Furthermore, many screening methods have a high rate of false positive results and confirmatory tests are usually only available through reference laboratories [22].

HTLV screening can only be recommended for endemic areas and in endemic populations [226] since a risk of infection may exist [148, 227]. The recently reported cases in the UK, of two recipients of kidneys from a common HTLV-1-infected donor, demonstrated infection in both individuals; incidentally, no risk factors were identified for the donor [228]. A group in Japan reported 100 % transmission rate in D+/R– living-donor kidney transplants (16/16), with 62 % incidence of HAM [229]. Because of further limited follow-up on recipients of HTLV-infected organs, no conclusive recommendations are possible [22]. In donor populations where HTLV is endemic – the Caribbean, most parts of South America, Africa, Asia (particularly the southern islands of Japan and Oceania, and also Iran) and Romania, as well as some higher-prevalence spots in some Chinese provinces, native populations in north Australia and some US states [230] – the risk assessment for donor-derived HTLV-infection should balance the following considerations: the likelihood of true HTLV-1 infection; the low likelihood of subsequent disease in recipients of such organs; the general shortage of organs; and the specific needs and wishes of patients.

In 2010, the US ceased mandatory testing for HTLV-1/2 [22]. Japanese experts suggest that HTLV-infected organs can be transplanted into previously infected HTLV recipients [231]. In Europe, HTLV-1/2 screening is mandatory only in France – despite a mere 0.0056 % sero-prevalence in new French blood donors [232] – and it is advised in Portugal. In the UK it is recommended in donors at increased risk for infection [50]. In Spain, it had been recommended for donors at higher risk for HTLV-1 infection (i.e. immigrants or sexual partners of immigrants from endemic areas, children at risk of maternal vertical transmission) [226, 229, 232] but more recent Spanish guidelines recommend to screen universally [89, 233]. An ECDC *ad hoc* expert panel recently suggested that if HTLV-1/2 screening is implemented in a member state or its regions for blood donations (e.g. due to high prevalence of HTLV-1/2 infections, exceeding 1 % in the general population or 0.01 % in first-time blood donors), it should also be implemented for tissue and cell donations [232].

Any initial reactive test result must be con-

firmed as a true positive for HTLV-1 before further conclusions can be drawn [232].

Anti-HTLV-1/2 screening should be attempted in donors coming from geographic regions with a high prevalence of HTLV-1/2 infections. D+/R– combinations are usually not accepted.

Caveat: a high rate of false positives has been documented with this test and should not be allowed to result in organ wastage.

8.6.2.17. *Human polyoma viruses*

The *Polyomaviridae* are a family of DNA viruses that infect a variety of hosts. BK polyomavirus (BKPyV) and JC polyomavirus (JCPyV) are human polyomaviruses that cause severe disease in immunocompromised patients. In cases of JCPyV and BKPyV, primary asymptomatic infection occurs early in life and persists as latent infection in the kidneys with occasional virus shedding in urine. When immunity is decreased, these viruses can reactivate, posing a threat to solid-organ transplant recipients.

BKPyV-associated nephropathy is a leading cause of renal allograft dysfunction and loss after kidney transplant [234-235]. However, it is still unclear whether BKPyV replication is a result of reactivation in the recipient's native kidneys or whether the virus originates from the allograft [236]. Though BKPyV sero-prevalence is too high to exclude seropositive donors from kidney donation, the potential high-risk constellation (BKPyV shedding in donors) should be analysed for clinical outcome in comparison with other risk factors for reduced transplant survival in future. Donor-derived BKPyV infection has been recently reported. Currently this issue is under investigation [237-239].

The issue of progressive multifocal leukoencephalopathy is addressed in section 8.9.

8.6.2.18. *Other viruses*

Donor-derived infections caused by rabies [1, 4] and lymphocytic choriomeningitis virus (LCMV, RNA-virus) [1, 4] have been reported. These rare infections cause life-threatening or fatal complications in recipients, without any possibility of curative treatment. Typical childhood infections may still occur in adulthood and can be transmitted through organ donation. Transmission of *Parvovirus* B-19 infection has been documented through bone marrow, blood and organ donation.

In many cases, no appropriate tests are available for screening. Some specialised laboratories can provide useful investigations, but only after a potential virus has been identified. The risk can only be assessed by careful donor evaluation, including the careful examination of travel and social history. Special attention must be paid to any unexplained behavioural or disease patterns (e.g. recent mental changes, unexplained fever, myalgia). This may be indicative of a rare or endemic infection restricted to a specific geographic area or population. In these cases, an awareness of unusual or rare infections is more important than the introduction of further screening assays without any benefits for recipients.

Please refer to section 8.11 on additional infectious diseases that can be transmitted by solid-organ transplantation.

8.6.2.18.1. Bornavirus

Germany has reported four human cases of acute encephalitis or encephalopathy caused by infection with Bornavirus 1 (Borna Disease Virus 1, BoDV-1; species Mammalian 1 Bornavirus [240]. This virus is clearly distinct from VSBV-1, Variegated Squirrel Borna Virus 1; species Mammalian 2 Bornavirus). The first investigations started at the end of 2016, and official notification of human cases was started in March 2018. Three of the cases belong to a cluster of solid organ recipients. The donor was from southern Germany and his cause of death was unrelated to neurological disease. At present, BoDV-1 disease among humans seems to be a rare event. However, further investigations into the frequency of such events are needed. In the transplant recipients, immunosuppression therapy likely has enabled and/or enhanced infection. The routes of transmission pertaining to the organ donor and the additional case remain unknown at this time. This is the first time that a possible BoDV-1 transmission through organ transplantation has been reported [241-243].

The risks are too low to justify uniform testing for rare or exceptional viral diseases. On the basis of information about the donor's recent behavioural/disease patterns and the present endemic situation in relevant regions, as well as the possibility of recent exposure, targeted testing and individual exclusion of donors should be considered.

Donors with encephalitis of unknown cause – especially when febrile – represent an exceptionally high risk of disease transmission and should be excluded until the cause of encephalitis has been identified for sure (e.g. see §8.9).

8.6.2.19. *Handling of acute emerging new viruses: influenza, Ebola, MERS-CoV and SARS-CoV-2*

8.6.2.19.1. Influenza

In 2009, pandemic A/H1N1-influenza virus infection occurred. This required a rapid action plan for an approach to potential organ donors possibly infected with the virus. Firstly, all available information was collected. Secondly, a guideline was issued. This initially occurred at a national level. Without proper testing methods, it was difficult to determine with enough sensitivity and specificity whether donors were not viraemic as in any case of influenza, and if a target organ was infected (e.g. lung or intestine). Therefore, it was assumed that, in the case of flu-like symptoms, this condition might have existed. Persons in contact with symptomatic people were considered at risk. Clinical symptoms guided the use of organs, as well as prophylactic anti-viral treatment, in donors and recipients, with oseltamivir (depending on resistance patterns).

When reliable screening methods became available, an appropriate diagnostic pathway was developed, which was still limited by the capacity for further investigations. Ultimately, donor inclusion or exclusion had to be done according to the newly developed pathway [12-13]. The next influenza virus pandemic may require new or adapted pathways. Such pandemic influenza infections will have to be distinguished from seasonal influenza.

For seasonal influenza in Europe, viraemia is unlikely. Therefore, organs from donors with seasonal influenza can be used, with the exception of lungs and intestine.

For non-novel viruses (i.e. all RNA-respiratory viruses currently circulating) in immunocompetent patients, no appreciable risk of transmission exists via the blood compartment. Respiratory viruses are only a reason for excluding the transplant of lungs. Screening of donors for respiratory viruses is only recommended if there is clinical concern.

For novel viruses, i.e. in the setting of the next pandemic influenza, organ donation should be excluded until information is available on the tissues where the virus replicates and on the prevalence of extra-pulmonary dissemination.

8.6.2.19.2. Ebola

In 2014 the Ebola virus emerged as a pathogen which has become endemic in some regions of Africa, raising concerns for the healthcare systems in other continents. Again, proper surveillance and obtaining of appropriate information were the key issues for avoiding infection spread, as well as the safety precautions of hygiene and deferral intervals including the time of incubation in persons at risk of acquired infection [244-246]. The minimum recommendation is to defer donors at risk due to exposure in the countries where Ebola is endemic, or related to other contacts, for two incubation periods (21-25 days doubled to 60 days). Donors who recover from Ebola virus infection should be deferred for one year to 1.5 years due to lack of proper evidence on viral persistence in the body.

8.6.2.19.3. MERS

The Middle East respiratory symptom coronavirus (MERS-CoV) is on the watch list as another potential risk [246]. Despite the ongoing transmission of MERS in Middle East [247], no case of transmission from organ donor has been reported thus far. There are only two reported cases of MERS infection in kidney recipients from Saudi Arabia [248].

8.6.2.19.4. SARS-CoV-2

Coronavirus disease 2019 (Covid-19) emerged in December 2019 in Wuhan, the capital of Hubei province, China. This highly contagious disease has spread across the world and throughout EU/EEA member states, with a daily increase in the number of affected people, confirmed cases and infection-related deaths as well as increasing numbers of protected people due to vaccination. Updated data are published daily on the ECDC [15] and World Health Organization (WHO) [16] websites. Covid-19 is an acute respiratory disease caused by a newly emerged zoonotic coronavirus. A positive-sense enveloped single-stranded RNA-virus, named Severe Acute Respiratory Syndrome *Coronavirus-2* (SARS-CoV-2), was isolated from a patient with pneumonia and connected to the cluster of acute respiratory illness cases from Wuhan. Genetic analysis has revealed that it is closely related to SARS-CoV and genetically clusters within the genus *Betacoronavirus,* subgenus *Sarbecovirus* [249]. Guidance regarding treatment and diagnostics in the general population overall is updated regularly by, *inter alia*, the Infectious Diseases Society of America [250]. Asymptomatic or presymptomatic viral shedding is well described with SARS-CoV-2 infection.

Transmission via droplet spread can occur from both symptomatic and asymptomatic individuals who are infected with Covid-19 [251]. In addition, it appears that patients with Covid-19 have the highest viral loads early in the course of their infection. Thus, a reliance on symptom-based screening strategies alone is not sufficient to prevent or diagnose infection; therefore consideration of symptoms and exposure history, with testing, is imperative.

While stool has tested positive for SARS-CoV-2 by nucleic acid testing (NAT), including PCR, it is not known whether this is replicative virus.

Since the beginning of the pandemic, the risk of transmitting SARS-CoV-2 from the donor to the recipient has been considered as a theoretical possibility. This has prompted ECDC and national and international professional societies and authorities to release guidelines for donor and recipient testing for SARS-CoV-2. All of them recommend that donors should be screened for suspected Covid-19 both epidemiologically and by clinical history; in addition, viral testing of at least one sample from the respiratory tract by NAT for SARS-CoV-2 must be performed before procurement. Especially when lung and/or intestinal donation is intended, viral testing by NAT is recommended on samples of the lower respiratory tract for SARS-CoV-2 (e.g. bronchial aspirate or BAL). At the time of writing, donor-derived transmission of SARS-CoV-2 has been reported in only three lung recipients from donors who had not been screened for SARS-CoV-2 RNA in respiratory tract samples [252].

Data regarding the safety of organ donation from donors with previous Covid-19 are extremely limited at this time. In this context, decisions whether to proceed with transplantation must include discussions with the transplant candidate and their proxy, as well as consideration of the risk associated with not proceeding with transplantation. There is broad consensus that organs from donors who have recovered from previous SARS-CoV-2 infection can be safely used for transplantation when the donor tests negative on NAT-based assays [253-257]. In Italy, organs from donors with previous Covid-19 can be used 14 days after the last negative PCR for SARS-CoV-2 with a negative BAL for deceased donors or nasopharyngeal swab for living donors prior to procurement. In Spain, for donors with a previous diagnosis of Covid-19, donation will proceed in cases with more than 14 days since the start of symptoms, more than 72 hours without symptomatology and a negative PCR. However, in cases where PCR is persistently positive, donation will be considered on a case-by-case basis, attending to severity of the disease, time since symptom onset, cycle threshold (Ct) values and anti-SARS-CoV-2 serology. At the time of writing (2020) it is not known how long-term sequelae after donor recovery from Covid-19 (e.g. heart, lung and kidney disease) might impact graft quality and recipient outcome.

Romagnoli *et al.* [258] have shown recently in a small series from Italy that livers from donors with SARS-CoV-2 NAT-reactive results from lower and/or upper airway specimens, but with no symptoms or only mild symptoms of Covid-19, can be transplanted into selected recipients with appropriate immunological protection and in dire conditions after informed consent. Hearts and kidneys have also been transplanted [258]. From this report, as well as ongoing research, the exclusion criteria for donors with SARS-CoV-2 NAT-reactive results obtained from the airways and without significant Covid-19 disease must be revised on the basis of accumulating evidence about the associated existing risk.

Current data show that organ transplant recipients are a high-risk population for infection with SARS-CoV-2 that may affect their morbidity and mortality [254-257]. The management of Covid-19 in the post-transplant setting presents complex challenges, emphasising the importance of strict prevention strategies.

Organs from deceased donors can be used for transplantation when clinical data indicate that the donor is not at significant risk of being infected and that NAT for SARS-CoV-2 is not reactive in nasopharyngeal swabs and/or samples from lower respiratory tract (in lung and intestine donors NAT from lower respiratory tract airways is mandatory). Research is ongoing to better define the risks associated with the use of organs (except lung) from donors with a reactive SARS-Cov-2 NAT result without significant symptomatic infection (recently), particularly in recipients with immunological protection.

8.7. Parasites, protozoans, nematodes

Active parasitic disease of the donor is a contraindication for organ donation. Exceptions may be possible if unacceptable risks for the recipients have been ruled out by transplant infectious disease specialists.

Prophylactic use of trimethoprim-sulfamethoxazole, atovaquone or combined antimicrobial therapy (including pyrimethamine dapsone and folinic acid, or pyrimethamine-sulfadiazine and other combinations) is known to be effective against *Toxoplasma gondii* as well as *Pneumocystis jirovecii* (*carinii*). It should be provided to organ recipients who are at risk of infection (generally, recipients of heart and vascularised composite allografts, which include muscle transplants) [34, 259]. Serology for toxoplasma is included in the standard screening of heart donors in order to avoid *de novo* infection through dissemination in a seronegative recipient

[259]. More than 70 % of the adult population in Europe has had contact with *Toxoplasma gondii*.

Persistent diarrhoea, colitis, etc., in donors – in combination with risk factors, for example recent foreign travel – should lead to investigations to exclude intestinal parasites. Usually, symptomatology is absent.

Donor-derived parasitic infections are rare in Europe, but must be considered for donors having contact with (i.e. through travel), or coming from, other areas. Details of tropical and geographically restricted infections during solid-organ transplantation have been previously published [260], and they are summarised in Table 8.8. For the most recent data about tropical and geographically restricted infections, especially in the case of donors with a history of foreign travel or a background of migration, transplant personnel are referred to the websites listed in section 8.2, where the most current epidemiological information can be obtained.

Detailed discussions of toxoplasmosis (§8.7.1), malaria (§8.7.2), Chagas disease (§8.7.3) and echinococcosis (§8.7.4) are provided below. In many parts of the world, endemic parasites such as *Strongyloides* spp. (e.g. Indian subcontinent, Africa) or *Schistosoma* spp. exist, with an elevated risk for donor-derived infection [261-262]. Due to migration and global travel or employment, there are sizeable populations at risk living in Europe. Screening of donors and/or empiric treatment of recipients and/or donors should be considered in all at-risk cases (see Table 8.8). Unfortunately, donors are often asymptomatic for such parasitic diseases.

Active parasitic disease in the donor is a contraindication for the use of organs. The possibility of parasitic infections should be considered in donors coming from, or having travelled to, endemic areas (see above-mentioned references and box entitled 'Websites', as well as Table 8.8) and in the case of persistent diarrhoea or other unexplained signs of illness.

For other infections by protozoans and nematodes, the risk-assessment approach for potential donors is equivalent to that applied to parasitic infections.

8.7.1. Toxoplasmosis

Toxoplasmosis is a worldwide parasitic zoonosis transmitted to humans by ingestion of raw or undercooked meat containing *Toxoplasma gondii* cysts or by ingestion of oocysts from faecally contaminated foods. Sero-prevalence of *Toxoplasma* varies geographically, with lower rates in the United States (3 %-35 %) and higher rates reported in western Europe, Africa, and South and Central America. The acute infection is followed by a latent chronic phase with persistence of the cysts in tissues, especially in the muscles, brain, eye and, more rarely, other organs [263].

Toxoplasmosis prophylaxis is standard following heart and heart-lung transplantation, where an increased risk of allograft-transmitted *Toxoplasma* is well recognised. In contrast, prophylaxis and routine serologic evaluation of donors and recipients for *Toxoplasma* in noncardiac solid organ transplantation (SOT) is generally not recommended. However, *Toxoplasma* IgG donor screening is now mandated by UNOS/OPTN policy [264]. In the absence of prophylaxis, the rate of transmission from a seropositive donor to a seronegative recipient (D+/R–) is maximal after cardiac transplantation, but cases have also been reported after liver and kidney and small bowel transplantation. Transmission of toxoplasmosis via liver transplantation is extremely uncommon but, in most cases, results in a fatal outcome [265-267]. The rarity of the disease and the non-specificity of the symptoms have led to a general lack of awareness among clinicians and, hence, a high mortality rate among transplanted patients due to the delayed initiation of therapy.

Toxoplasmosis is transmitted via an infected allograft from an IgG seropositive donor to a seronegative recipient. The high mortality rate is generally due to a delay in diagnosis and initiation of therapy. The classic diagnosis of toxoplasmosis based on serological tests can be unreliable in transplant patients. Therefore, the diagnosis is usually based on the direct demonstration of the parasite in tissues or biological fluids. However, these techniques are time-consuming and lack sensitivity. The PCR technique allows a simple, rapid and highly sensitive detection of *T. gondii* DNA in various specimens and represents a valuable diagnostic tool for assessing disseminated toxoplasmosis [268-269]. In a multicentre case-control study from Spain, a negative serostatus prior to transplantation was the only independent risk factor for toxoplasmosis [270]. In fact it has been documented that the liver is a frequent site of cyst carriage, confirming that transplantation of an organ from a seropositive donor to seronegative recipient is at high risk for transmitting toxoplasmosis. Seronegative solid organ transplant recipients receiving a graft from a seropositive donor are at high risk for developing toxoplasmosis and should be given prophylaxis and receive careful follow-up [271-272].

8.7.2. Malaria

Malaria is an acute febrile infection caused by five species of *Plasmodium*: *P. falciparum*, *P. vivax*, *P. malariae*, *P. ovale* and *P. knowlesi*. The disease causes about 200 million cases and 400 000 deaths each year, mainly in the African region (responsible for 93 % of malaria cases reported in 2018) [273].

Systematic monitoring of donors and recipients from endemic areas is mandatory because of the high incidence of asymptomatic low parasitaemia in semi-immune individuals, the risk of occult liver stage of the hypnozoite (related to *P. ovale* and *P. vivax*) for liver donors and recipients, and the fact that, with no treatment, the parasites can persist for long periods – usually 2 years for *P. falciparu*m, 3 years for *P. vivax* and *P. ovale*, and up to 40 years for *P. malariae* [274-277].

Parasitaemia may be detected by blood smears, liver biopsy, PCR or antigen assays. In some donors, symptoms may not be detectable. There should be no delay in the initiation of anti-malarial treatment if malaria is suspected in either a donor or a recipient. Donors at risk of malaria infection include residents of, immigrants from and travellers to endemic areas.

According to the UK SaBTO guidelines [50] asymptomatic deceased donors with residence in or travel to endemic areas more than one year ago can be accepted as donors; febrile donors with a recent travel history to a malaria-endemic country require a parasitaemia screening test before donation. If a donor was born or has lived in a malarious area for more than 6 months, at any time of life, a validated anti-malarial antibody test should be performed, but, in the case of deceased organ donors, donation may proceed pending the results. If the test is reactive, a NAT test should be performed. If there is a history of travel within the last 4 months, living donors should be deferred and deceased donors should be screened through serological and NAT tests. If the history of travel is between 4 months and one year, a validated anti-malarial antibody test should be performed; if the test is reactive, a NAT test should be done. The results should be available within 24 h post-transplant in order to initiate further measurements.

Other guidelines suggest also [26] that PCR should be performed, as it is the most sensitive test to detect parasitaemia compared to Giemsa-stained thick blood smear and rapid diagnostic test (RDT). If PCR is unavailable, microscopy (visualisation of parasites in stained blood smears) and RDT can be performed with the known significant limitations. RDTs have lower sensitivity, especially for non-*Plasmodium falciparum* malaria, and their use as a screening test cannot be recommended [278]. In consideration of South American recommendations [279], it should be noted that the parasite can persist for longer periods in semi-immune individuals from malaria-endemic areas in the absence of symptoms (e.g. *P. malariae*). This requires consultation of transplant infectious disease experts. Also infection by different *Plasmodium* species may exist.

Parasitaemic donors are usually rejected by transplant centres. Grafts can be used after successful treatment and recovery of the donor, but it must be remembered that some species (*P. vivax* and *P. ovale*) may survive in the liver. In such situations, the recipients must be followed up to promptly detect low parasitaemia and provide early treatment. If there is not enough time to treat the parasitaemic donor before the donation, treatment of the recipient is recommended.

Differential diagnosis of any fever in the recipient within the first six months after transplant should include the possibility of reactivation of malaria in recipients of grafts from donors at risk of acquired malaria. Proper treatment of the recipient must be initiated immediately [280]. Treatment recommendations are dependent on the *Plasmodium* species and the geographic region where malaria was acquired. Consultation of a transplant and malaria/tropical medicine specialist is recommended.

If parasitaemia in the donor or recipient is detected, prompt treatment must be initiated according to the Plasmodium species. Treatment of the donor should be continued in the recipient.

In donors at risk for asymptomatic malaria infection (see text above), NAT for detection of low-level parasitaemia and antibody test should be performed within 24-48 h post-transplant in order to initiate further measurements.

Although it is rare, donor-derived malaria may occur, irrespective of donor history, and should be considered in patients with persistent fever and if other infections have been ruled out.

Consultation of a transplant infectious disease expert is recommended.

8.7.3. Chagas disease

Chagas disease (or American trypanosomiasis) is a vector-borne infection caused by the protozoan *Trypanosoma cruzi*. Although the disease is endemic in Latin America, its geographic distribution has changed due to immigration of asymptomatic infected individuals from endemic to non-endemic regions.

Chagas disease is characterised by an acute and a chronic phase. During the acute phase the

patient usually presents with an asymptomatic high parasitaemia that is progressively controlled after a few months without treatment; untreated infection can progress to a chronic form of the disease characterised by low parasitaemia, which may remain asymptomatic for life or progress to cause irreversible cardiac, gastro-intestinal or peripheral nervous system disease due to the parasite predilection for muscle, heart and neurological cells.

In the transplant scenario, Chagas disease can occur as an acute infection among sero-negative or uninfected recipients receiving an organ from a sero-positive or previously infected donor, or can occur as a reactivation parasitaemia among positive recipients due to post-transplant immunosuppression.

T. cruzi antibody screening should be undertaken in donors who meet any of the following criteria: born in Latin America; have received blood components or products while resident in Latin America; lived in rural subsistent farming communities for a continuous period of 4 weeks or more in Latin America; or whose mothers were born in Latin America [50].

Asymptomatic parasitaemia is more common than symptomatic disease in potential donors [259, 281-282]. Antibodies against *Trypanosoma cruzi* indicate previous exposure and current infection, unless treated. Due to significant variability in sensitivity and specificity, appropriately validated tests must be used. Serological tests are based on conventional (enzyme-linked immunosorbent assay, ELISA; indirect immunofluorescence assay, IFA; or indirect haemagglutination assay, IHA) and nonconventional methods (such as recombinant antigen ELISA and Western blot with trypomastigote excretory-secretory antigen, TESA-Blot). Due to the limited sensitivity and specificity of conventional tests, the serological diagnosis should be based on different tests performed in parallel [283].

Acute parasitaemia may be detected by PCR and Strout test (microscopy of blood after blood concentration), but these tests are generally not sufficiently sensitive for screening of organ donors because of intermittent parasitaemia. For screening purposes, serology with validated antibody assays must be used.

The use of kidney, liver, lung and pancreas from donors with chronic Chagas disease is possible. Cardiac or intestinal grafts should not be used from donors with a history of *Trypanosoma cruzi* infection, whereas other organs can be considered [72-75, 81-83, 85-86, 259-262, 280-284]. The risk of *T. cruzi* transmission is about 10 % to 20 %.

Prophylactic treatment (benznidazole) in D+/R– combinations is considered controversial but it has had some success [285]. All recipients of organs from Chagas disease-positive donors should be closely monitored for disease transmission by PCR or microscopy of blood [284], independently of use of prophylaxis. Treatment (benznidazole, nifurtimox) should be initiated promptly upon recognition of parasitaemia as a pre-emptive therapy. Some experts recommend avoiding certain immunosuppressive therapies (e.g. thymoglobulin or mycophenolate) in recipients of organs from Chagas disease-positive donors [72]. After treatment of acute infection acquired from the donor, the patient should restart monitoring with clinical and parasitological periodical evaluation for an indefinite period because there is no consensus for cure.

8.7.4. Echinococcosis

Echinococcosis (critical in liver or lung donations) requires an individual-based decision [7]. If there is evidence of disseminated echinococcosis in the donor, then organs should not be considered for transplant. Even if previous surgery and therapy has been successful, some transplant centres do not recommend the use of affected organs (e.g. an affected liver lobe), while other organs may generally be used with a low risk of transmission. *Echinococcus* has been detected in rural areas throughout Europe, with donors being unaware of antecedent infection. Extra-hepatic manifestation of hydatid cysts should be ruled out [7].

8.7.5. Helminths: nematodes, trematodes, cestodes

Intestinal nematodes either stay in the intestine (e.g. *Trichinella*) or, during their life-cycle, they can disseminate via the blood from the intestine to the lungs or other tissues (e.g. *Ancylostoma*, *Ascaris*, *Strongyloides* or *Schistosoma*) with an increasing number of donor-transmitted cases [286]. In addition, some nematodes can be transmitted by *Culex* or *Anopheles* mosquitoes (e.g. lymphatic filariasis through *Wuchereria bancrofti* and *Brugia* spp., *Mansonella*), black fly (e.g. *Onchocerca*) or tabanids (e.g. *Loa loa*) and may persist in the body for months (e.g. filariae) [287]. Nematode infections are endemic in tropical countries, so a history of travelling to or coming from such areas, plus reported visual impairment and itching, may suggest infection. As long as the life-cycle can be interrupted by preventing the transmission of microfilariae via the blood from donors to non-immunosuppressed recipients, no disease development may be expected. Active infec-

tion should preclude donation, although evidence on how to manage donors with these infections is limited.

There should be a high index of suspicion for parasitic infections not only in donors and recipients coming from endemic regions in the world but also in Europe. Therefore, screening should be considered in potential donors at elevated risk (antibodies). Otherwise serious unexpected donor-derived infections may be missed [288-289] whereas pre-emptive administration of ivermectin may prevent such a complication when the screening result becomes available. The prevalence of *Strongyloides* infection of 12.4 % has been reported among farm workers in a Mediterranean region in Spain [290]. Infections by one of the multiple trematode species (e.g. *Schistosoma*) are most common in Asia, Africa, South America or the Middle East. In 2014, 11 cases (6 from France and 5 from Germany) of uro-genital schistosomiasis were reported. All cases were exposed to fresh water in a natural swimming area in southern Corsica (Cavu River) [291]. There have been isolated cases of *Schistosoma mansoni* transmission through infected liver transplantation and a possible reactivation of schistosomiasis in patients with chronic infection originating from endemic areas, who received uninfected liver transplants [292]. In both situations, transplant recipients were successfully treated with praziquantel.

Infections by cestodes (e.g. *Cysticercosis*, *Echinococcus*) or other tapeworms are common in underdeveloped countries, or those having poor sanitary conditions, or endemic in specific geographical regions (see §8.11).

Recently, in the UK, a rare case of fatal donor-derived nematode transmission (*Halicephalobus gingivalis*) to kidney recipients was the subject of a lay press release [293]. Also, parasitic infection by pathogens unknown in Europe may occur in donors coming from distant countries or having lived there (e.g. clonorchiasis in a donor having migrated from Kazakhstan to Europe [294].

Target organs of active infection by helminths should not be used for transplantation. Since knowledge is limited, it is recommended to consult transplant infectious disease experts.

8.8. Prion-related diseases

Transmissible spongiform encephalopathies are rare, but exclusively lethal, degenerative diseases of the central nervous system [7]. Creutzfeldt–Jakob Disease (CJD) and variant Creutzfeldt–Jakob Disease (vCJD) are transmitted by prions. Prions result from abnormally-folded proteins, so there are no NAT assays available, nor are there sensitive Western blot or ELISA assays for the detection of prion proteins in the blood. Diagnosis can only be made, if at all, *post mortem* on autopsy material. It is suggested that transplant teams should adhere to CDC recommendations (www.cdc.gov/prions/) and consider the risk of transmissible spongiform encephalopathies being transmitted in cases where:

a. CJD or vCJD has been observed frequently within the family;
b. treatment has occurred with pituitary gland hormones or growth hormone of human origin;
c. *dura mater* has been used during an operative procedure.

Currently, there are no definitive conclusions about the risk of people being infected in Europe. Living in or having travelled to the UK is associated with this risk, but evidence is lacking about the extent. It is recommended to obtain informed consent of the recipient about this when such at-risk grafts have to be used. Future monitoring of this issue will be required for further evidence.

Dura mater should not be procured and used as graft material due to an unpredictable risk of prion transmission.

8.9. Cerebral infections (meningitis/encephalitis) by various pathogens

Any meningitis or encephalitis caused by an unknown pathogen is an absolute contraindication for organ donation. A brain abscess is not *per se* a contraindication. Nevertheless, the potential causes of the brain abscess should be evaluated before accepting the organs.

Extreme precaution should be taken in cases of donors with presumed bacterial meningitis when no pathogen can be identified in cerebrospinal fluid or blood by culture or PCR. All data on the 'safety' of donors with meningitis are in the context of positive cultures as outlined in section 8.4.2. Further, there have been transmissions of malignancies and infection (e.g. TB, fungi) when donors with culture-negative, presumed bacterial meningitis were used. Therefore, donors with presumed bacterial meningitis should only be used when there is a proven bacterial origin or possible *Naegleria fowleri* infection.

In the case of a non-reactive culture but where the bacteria are confirmed by PCR as the pathogen causing the meningitis (e.g. Liquor-PCR), it can be

assumed that, after 24-48 h of antibiotic treatment, infection will not be transmitted – as long as all other clinical data fit. Still a residual risk of unconfirmed disease exists.

If there is no pathogen identification, including by PCR, organs should not be used for transplantation. Before the donor is rejected, the particular case should be discussed with a transplant infectious disease expert.

As already outlined in the section about specific virus infections (see §8.6.2), donors with encephalitis, particularly febrile encephalitis, present an exceptionally high risk for disease transmission and should generally be excluded unless the pathogen is identified and viraemia can be excluded, and treatment options in the recipient exist.

In the case of a potential donor who dies of confirmed herpes encephalitis and received initial treatment, the use of the organs can be recommended, provided that the donor is not viraemic (viraemia is rarely found in HSV encephalitis) and provided that the recipient is HSV-seropositive pre-transplant. If the recipient is seronegative, specific anti-viral prophylaxis is recommended for 6 months.

Progressive multifocal leukoencephalopathy (PML), caused by JC virus and its mutants, is typically observed in immunocompromised patients and is associated with high viral load in the cerebrospinal fluid (and urine) but in general without viraemia. Currently there are not enough data to endorse acceptance of organs from a donor with PML. The number of potential donors with PML is very limited and they should be excluded from donation until more reliable data become available.

Acute disseminated encephalomyelitis is always diagnosed by exclusion of other causes. But unfortunately, it has been associated with donor transmissions, including rare pathogens, e.g. *Balamuthia mandrillaris* [295].

A special donor population is represented by those with unrecognised central nervous system (CNS) infection. Unrecognised CNS infection in donors has been associated with high rates of transmission to organ recipients, with subsequent morbidity and mortality. These events are of great concern due to the absence of effective treatments for most of these pathogens. To help OPOs and transplant centres to differentiate CNS infections from stroke in potential donors, the Donor Transmitted Advisory Committee created a document to outline indicators of possible meningo-encephalitis in potential deceased organ donors. Concerted efforts to improve screening of donors with suspected encephalitis, to carefully consider risks and benefits of transplanting organs from these donors and to better monitor transplant recipients for rapid recognition of infection may improve patient management and prevent further transmission [296].

The key questions summarised in Table 8.7 should be asked about any potential donor [296] in order to mitigate the risk of missing an unsuspected CNS infection.

There is still a considerable overlap between findings in donors with and without CNS infection (e.g. fever), but one upshot in most cases of donor-derived transmission of CNS infection was that suspicion of it was missed. Most reports about unintended transmissions of CNS infection result from cases where either the diagnosis had been missed or where the pathogen was not identified for further risk assessment. In cases of a known pathogen with curative treatment performed, either in the donor or recipient, a low rate of adverse outcomes can be postulated, as data from a UK Transplant registry study show [297].

Any meningitis or encephalitis caused by an unknown pathogen is an absolute contraindication for organ donation. Before the donor is discarded, the particular case should be discussed with a transplant infectious disease expert.

8.10. Pitfalls of serologic screening

8.10.1. Unexpected results

In the case of an unexpected result (e.g. reactive anti-HIV-1/2 testing), the appropriate response depends on the risks for the patients (both donor and recipient) and staff involved:

- the donation procedure must be interrupted and no organ or tissue should be procured until confirmatory test results are available (e.g. reactive anti-HIV-1/2 testing); or
- the donation procedure may be continued under the assumption that the donor is infected and will transmit the virus with acceptable harm to other patients after appropriate recipient selection (e.g. D+/R+ combinations). This requires time for a new organ-allocation procedure, but without the need to wait for confirmative tests; or
- the donation procedure may be continued, including procurement, under the assumption that an infection can be managed at the recipient transplant centre (e.g. reactive anti-CMV testing).
- However, if a donor has recently received transfusions of blood, blood components or intra-

venous immunoglobulin preparations, then antibodies may be acquired passively, which may cause false positive results. If no pre-exposure specimen is available, it is impossible to provide an unbiased result. Then reactivity might be assumed without knowledge whether this is associated with the donor or a blood product.

8.10.2. Haemodilution and quality of specimen investigated

Whenever possible, a donor blood sample collected before administration of any transfusions and infusions should be used for testing purposes. However, it is recommended to collect such blood samples within the 96 h before procurement (or even closer provided that results are available before procurement); donor samples should also be taken < 24 h before procurement and archived [27]. This latter statement may help to reduce the risk of missing window-period infections – but the conflict of issues becomes obvious.

If a donor has recently received significant amounts of transfusions of blood components, or infusions of colloids or crystalloids due to substantial loss of own blood, testing of donor blood collected post-transfusion or post-infusion may not be valid due to dilution. When, for example, low-level viraemia exists, which is about the lower threshold for specific NAT diagnostics, then measurement may become influenced. In contrast to this consideration, the recent PHS guideline excluded donor haemodilution as a risk factor, because only one case of disease transmission in 1986 (HIV) could be attributed to this issue and nowadays the methods used – especially NAT – have a higher and sufficient sensitivity [27]. Further, 50-60 % of human IgG is distributed throughout the tissues outside blood vessels and is recycled back into the bloodstream within 48 h [298]; therefore serologic tests become possible again without major concerns about significant haemodilution.

Careful assessment of the extent of the donor's dilution that might render a test result invalid includes the use of a formula to calculate dilution of the donor's original circulating blood volume (and circulating levels of antigen and/or antibody, if present) as well as knowledge of the limitations of the test used and the results expected. Examples of when a haemodilution calculation may need to be carried out include:

- *ante mortem* blood sample collection: if blood, blood components and/or colloids were administered in the 48 h preceding blood sampling, or if crystalloids were infused in the hour preceding blood sampling;
- *post mortem* blood sample collection: if blood, blood components and/or colloids were administered in the 48 h preceding death (circulatory arrest), or if crystalloids were infused in the hour preceding death (circulatory arrest).

Refer to Figure 8.6 for an example of a commonly used formula to assess the donor's potential haemodilution or plasma dilution that can be applied when the donor has lost blood [299-303]. Adaptations of the algorithms may be needed for body sizes outside the normal adult range. Allowances may need to be made for very large or very small adult donors, or for paediatric donors.

Ultimately, it is important to consider that calculating the degree of dilution only by one of the currently used formulas [300-301] does not take into account pathophysiological changes due to blood and volume replacement in organ donors. In deceased organ donors, maintenance protocols encourage replacement of the blood volume by fluids, which results in a lower haematocrit than in healthy adults according to the standards of intensive care medicine accepting haemodilution (see Chapter 5). Therefore, the recipient team should perform a proper risk–benefit assessment to evaluate the risk of a false negative result due to haemodilution judged against the potential benefit to the recipient [302] after being properly informed about which assays have been used to determine the results.

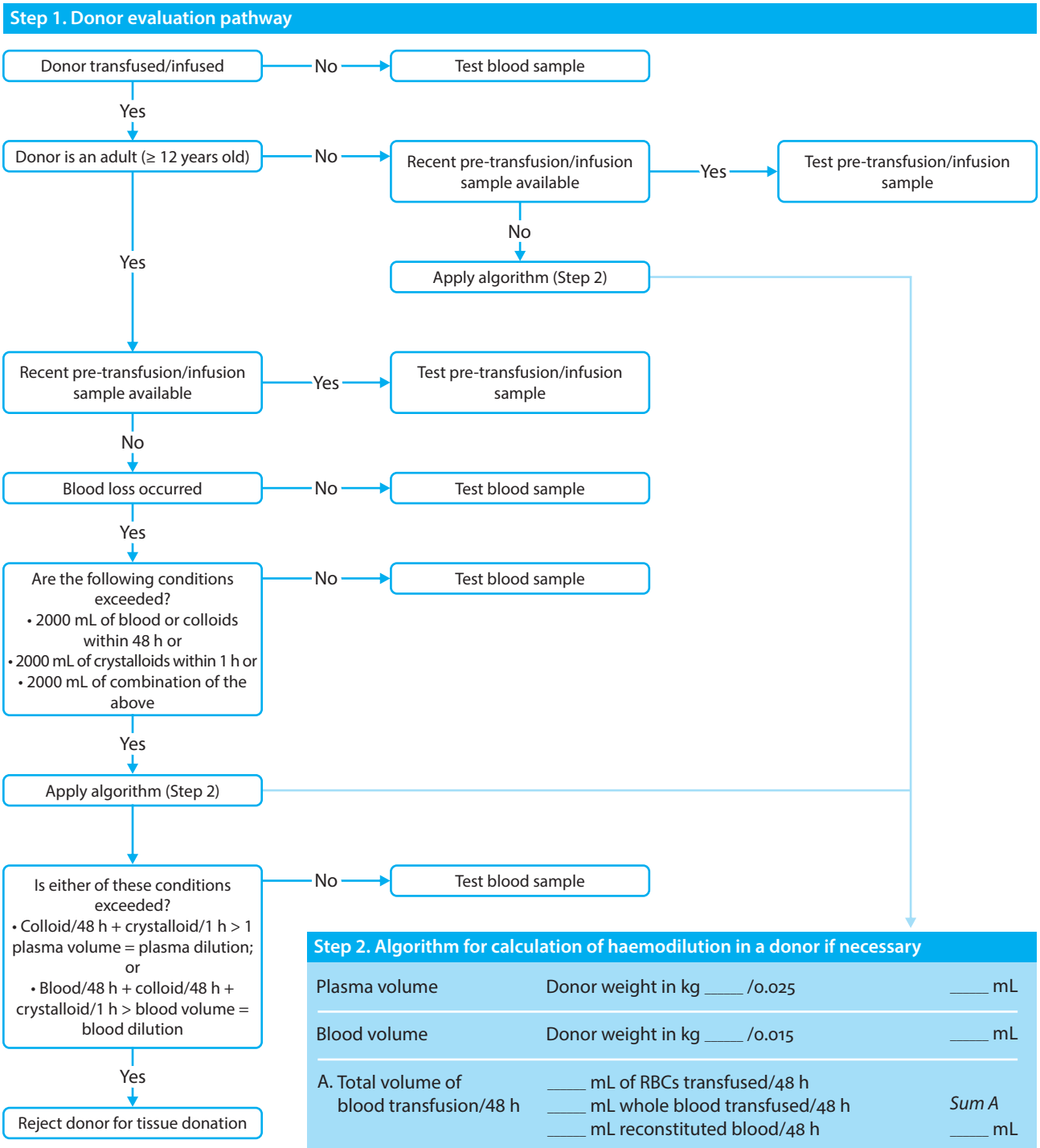
Finally, the quality of the specimen sent for testing is important (no haemolysis, proper storage, no dilution when sample is drawn from donor) [303].

8.10.3. False negative and false positive results

A false negative result means that a test does not detect infection where an infection exists, because of haemodilution, a window-period infection, incorrect sampling or inappropriate test quality.

A false positive result means that a test wrongly indicates reactivity to infection where an infection does not exist and may arise due to contamination, quality control issues, cross-reactivity or inappropriate test quality.

Figure 8.6. **Recommended steps for the calculation of haemodilution**



Source: Based on the algorithm developed by the Food and Drug Administration, USA [297].

Table 8.7. **Key questions to be asked of any potential donor to mitigate the risk of missing an unsuspected central nervous system infection**

Donor characteristic	Comments
Cerebrovascular accident in a patient without risk factors	Especially in young adults or paediatric patients without known risk factors for severe complications due to cerebrovascular damage, CNS infection may be associated with a cerebrovascular accident
Fever at presentation of illness or at admission without clear explanation	Early fever with changes in mental status would be higher-risk; fever is common after hospitalisation and non-specific in critically ill patients
Altered mental status/seizure at presentation illness/admission	Higher risk would include potential donors with new and otherwise unexplained seizures or mental status changes
CNS Imaging characteristics	There may be significant overlap with non-infectious causes of CNS disease
Cerebrospinal fluid abnormalities	Higher-risk findings include unexplained CSF pleocytosis, low glucose and elevated protein; low cellularity in CSF does not exclude an infectious process and can be often seen in viral encephalitis, particularly in the early stages
Immunosuppressed host	Examples include treated autoimmune disease, cirrhosis (risk factor for cryptococcosis)
Environmental exposures	Examples include exposures to bats or other potentially rabid animals, significant exposure to mosquito or significant exposure to TB infection (with/without MDR TB)

CNS: central nervous system; CSF: cerebrospinal fluid.

Source: Kaul, Covington, Taranto *et al*. Solid organ transplant donors with central nervous system infection [296].

8.10.4. Blood samples drawn after cardiac arrest

Blood samples taken for screening before cessation of circulation, in donors after circulatory death, are always preferable to those obtained afterwards (see Chapter 12). A procedure should be in place to ensure identification of, and easy access to, stored donor samples at each hospital. If such blood samples are not available, samples should be taken as soon as possible after the cessation of circulation, i.e. within 24 h. To avoid further haemolysis, the samples should be centrifuged and the serum or plasma separated as soon as possible after collection. Whenever such blood samples are investigated, the test employed has to be validated for such samples and the laboratory must be informed of the nature of sample collection.

8.10.5. Procurement from newborns

In infants younger than 6 months old, serologic screening may be unreliable due to the transfer of maternal IgG. Maternal IgG may persist up to 18 months after birth. Complementary serologic screening of the mother or NAT of the infant donor will clarify the risk of vertically transmitted diseases. If this is impossible, the donor should be used with caution, or infection should be ruled out by NAT. IgG antibodies may also be transferred from mother to child by breastfeeding. Due to the limited amount of blood specimen available for testing in newborns, each centre should have a protocol on how to handle such situations.

8.10.6. Donor sample archive

Samples of relevant donor material (e.g. serum, remains from HLA-typing) should be stored for a period of at least 10 years for retrospective studies if indicated (see chapters 6, 11, 15 and 16). The 2020 PHS guideline recommends storage of serum and ethylenediaminetetraacetic acid (EDTA) specimens for serologic and NAT testing [27].

8.11. Geographic restrictions

Table 8.8 is a non-exhaustive overview of geographically restricted, rare or critical infectious diseases that can be transmitted by solid-organ transplantation; the table is modified from the original sources [5, 260]. As therapies for infections change, it is recommended to discuss with an infectious disease specialist the status of each donor presenting with a suspected infection. The 'Remarks' column provides information on what risks are known to exist, whether donors may be used in cases of infection, what to do in case of transmission and comments on the relevance in Europe.

Beyond these geographic considerations, risks for infections should also be evaluated according to lifestyle, living and sanitary conditions, vertical transmission, vaccination record, etc. (see tables 8.8, 8.9). Other viruses with oncogenic potential are summarised in §9.8 (Table 9.5). Finally, surveillance of disease-transmission vectors contributes to detecting new transmission risks.

Table 8.8. **Geographically restricted, rare or critical infectious diseases**

Disease (pathogen)	Geographic distribution, endemic zones and risks	Remarks	Transmission reported*
Aspergillosis (*Aspergillus* spp.)	Worldwide Risk factors: prolonged stays in hospital (ICU), immunocompromised, building renovation, damp conditions	Donors with invasive and disseminated Aspergillosis should not be used	Yes
Bacterial infections (various): a) *Staphylococcus aureus*, *Pseudomonas* spp. b) *E. coli, Yersinia enterocolitica, Brucella* spp., *Bartonella* spp., *Enterobacter* spp., *Acinetobacter* spp. c) *Bacteroides fragilis, Klebsiella* spp. d) other species	Worldwide	a) Risk of mycotic aneurysm a) to d) Pulmonary and other infections d) See specific pathogen See also §8.4.1, §8.4.2, §8.4.3, §8.4.5, §8.4.7	Yes
Babesiosis (*Babesia* spp.)	Worldwide,including eastern and western USA; especially subtropical climates	Transmission from infected blood and organ donors described No precise exclusion criteria for organ donation	Yes
Blastomycosis (*Blastomyces dermatitidis*)	North America (Mississippi and Ohio river, Great Lakes), Central America and Mexico	Serologic tests and urine antigen assays may distinguish between acute or reactivated infection in donors and recipients from endemic areas. Probably no risk for previously infected recipients. No precise exclusion criteria for organ donation described. Prophylactic use of azole anti-fungal drugs may reduce the incidence of donor-derived disease if infected donors are used	Yes [304]
Bornavirus		Ongoing research (see §8.6.2.18)	Yes
Lyme disease (*Borrelia* spp.)	Endemic in areas with ticks (northern hemisphere); various species of *Borrelia* in Europe	Check donor history: tick bites, *erythema migrans*, neurologic failures, neuroborelliosis, arthropathy. After successful treatment, donation may be possible	
Candidiasis (*Candida* spp.)	Worldwide	Donors with disseminated or invasive disease should not be used	Yes
Chikungunya fever (*Chikungunya virus*)	Africa, India, Southeast Asia, America; emerging in many European regions with warm climates	Transmission via diurnal *Aedes* spp. mosquitoes. Monitor recipients of grafts from donors with reactive serology. Donors with positive NAT test (viraemic donor) or clinical symptoms compatible with Chikungunya should be excluded for 28 days from the positive test or the onset of symptoms	Theoretically possible; not described yet
CMV infection (*Cytomegalovirus*)	Worldwide, contact with virus varies from country to country (60-100 % prevalence)	Virological monitoring and pre-emptive treatment or anti-viral prophylaxis should be considered in all patients (new infection of naïve recipients must be avoided). Donors without active CMV disease (viraemia) can be used	Yes
Coccidioidomycosis (*Coccidioides immitis*)	Southern USA, Mexico, Guatemala, Honduras, Nicaragua, Venezuela, Colombia, Argentina, Paraguay	Serologic tests and urine antigen assays may distinguish between acute or reactivated infection in donors and recipients from endemic areas. Probably no risk for previously infected recipients, but provide azole prophylaxis. Lung transplant: if donor comes from endemic areas, initiate azole prophylaxis in recipients for 6 months unless infection excluded	Yes

* Transmission reported by solid-organ transplantation: Yes = reported, No = not reported, but high probability of transmission without documented cases or where data are lacking for robust conclusions.

Disease (pathogen)	Geographic distribution, endemic zones and risks	Remarks	Transmission reported*
Coronavirus Disease 2019 (Covid-19): Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2)	Global pandemic since 2020	Test nasopharyngeal swab and BAL donors by NAT for SARS-CoV-2. If not reactive and if clinical data are not indicative for infection, donors can be used (August 2020). Ongoing research for further conclusions.	Yes
Coronavirus family	SARS-CoV: Asia, China MERS-CoV: Middle East	Further harmful viruses exist: SARS-CoV, MERS-CoV (see §8.6). Beyond this, other harmless coronaviruses exist, causing minor respiratory infections	
Q fever (*Coxiella burnetii*)	Worldwide, with regional variation in Europe: localised occurrences around farms with infected animals (e.g. sheep, goats). Migrating herds contribute to further spread	Targeted antibiotic therapy might prevent outbreak. Spread occurs by aerosol over many kilometres or after preservation in any medium over months. PCR (polymerase chain reaction) and serology at specified laboratories	No reported cases yet
Cryptococcosis (*Cryptococcus neoformans*)	Worldwide	Donors who died with meningo-encephalitis caused by *Cryptococcus* should not be used. *Cryptococcus* antigen tested in blood or by ligase chain-reaction assays. No precise exclusion criteria for organ donation described in other cases	Yes
Cryptosporidiosis (*Cryptosporidium* sp.)	In slums: 65 % prevalence in developing countries, 20-30 % in developed countries	Faecal-oral infection; suspected if profuse, watery diarrhoea occurs. No known effective therapy. Indirect immunofluorescence, antibody-ELISA assays	No
Cystoisosporiasis (*Cystoisospora belli* syn. *Isospora belli*)	(Sub)-tropical South America, Africa, Southeast Asia	Causes diarrhoea. Trimethoprim-sulfamethoxazole and reduced immunosuppression resolve infections in recipients	No
Dengue virus infection	Temperate areas of Asia, Africa and America; may spread to 'warmer' regions in Europe	Transmission by *Aedes* mosquitoes. NAT or NS1-antigen test for detection of viraemia. Transmitted infection may results in fatal complications. Donors with positive NAT test (viraemic donor) or clinical symptoms compatible with Dengue fever should be excluded for 28 days from the positive test or the onset of symptoms	Yes
Ebola virus	Tropical Africa	Significant risk of transmission in persons at risk for acquired infection during incubation period (21-25 days)	
EBV infection (Epstein–Barr virus)	Worldwide, > 90 % of all adults latently harbour the virus	PTLD is a major risk; PCR monitoring of recipients, *de novo* infection of naïve recipient requires critical follow-up. Donors without active EBV disease (infectious mononucleosis) can be used.	Yes
Echinococcosis (*Echinococcus* spp. e.g. *Echinococcus granulosus*)	Worldwide, Mediterranean and rural areas of Europe, South America, southern Russia, central Asia, China, Australia, Africa	No precise exclusion criteria described. Without active infection and dissemination beyond the liver (calcified cysts), organs can be used. Therapy possible. People are often unaware of antecedent infection	Yes
Amoebiasis (*Entamoeba histolytica*)	Insanitary conditions (food, water) especially in Central and South America, Asia, Africa	No precise exclusion criteria for organ donation described. Check donors living in insanitary conditions (food, water) and/or coming from areas of risk and/or with a history of dysentery or diarrhoea or colitis (serology, faecal PCR, microscopy; parasite mostly limited to intestines, but liver abscess or dissemination possible). Critical organs: liver, intestine	No

* Transmission reported by solid-organ transplantation: Yes = reported, No = not reported, but high probability of transmission without documented cases or where data are lacking for robust conclusions.

Disease (pathogen)	Geographic distribution, endemic zones and risks	Remarks	Transmission reported*
Hantaviral diseases (*Hantavirus* spp.) Worldwide: the different species are grouped as old-world (causing hantavirus haemorrhagic fever with renal syndrome: HFRS) and new-world (causing hantavirus cardiopulmonary syndrome: HCPS)	Europe: *(Puumala-, Dobrava-Belgrade-, Saaremaa-, Seoul- and Tula-virus)* endemic in many regions. Rodent faeces contain the virus (aerosol transmission), infection causes HFRS of variable degree [305-306]. Europe/Asia: *Hantavirus* species often associated with HFRS; Other regions: Hantavirus species often associated with HCPS	Europe: Consider specific diagnostics in cases of acute renal damage (reversible) associated with fever, pain, thrombocytopaenia and/or capillary leak (± nonrenal organ failure) [305-306]. After recovery from acute infection, organ transplant should be possible. Worldwide: Depending on the virus species, different organ systems are affected with risk of human-to-human transmission in a few species	
HAV infection (hepatitis A virus)	Worldwide, poor sanitary conditions. Recurrent ongoing outbreak (in MSM population) due to sexual transmission	After recovery from acute infection no transmission reported. One report of transmission (see §8.6.2.10)	Yes [153]
HBV infection (hepatitis B virus)	Worldwide Prevalence of anti-HBc reactive > 50 % in Asia, South Pacific, sub-Saharan Africa, Middle East; Prevalence of anti-HBc reactive > 10 % in eastern Europe, Mediterranean, Inuit. People HBsAg-reactive are infected with: Genotype A (which is the reference of the WHO Standard for HBV-testing): North America, northern Europe, South Africa (≈ 3 million people); Genotype B/C: Japan, east Asia, Australia (≈ 240 million people); Genotype D: Russia, India, West Africa, Middle East, Mediterranean (≈ 40 million people); Genotype E: West Africa (≈ 1 million people); Genotype F: South America (≈ 3 million people)	Avoid new infection of naïve recipients. If transplantation is done, anti-viral therapy and HBIG prophylaxis is mandatory plus follow-up. HBV-infected recipients require anti-viral therapy anyway. Check for latest therapy recommendations and development of mutants. Genotype not relevant for risk of infection and therapeutic responses, but may alter serologic results (HBeAg and/or anti-HBe-negative HBV infections). Use donors according to case-based decisions. In emergency situations, organs from viraemic donors have been used with anti-viral therapy and anti-HBs-hyperimmune globulin prophylaxis in the recipient. In HBV-viraemic donors, transmission can occur with any graft. In non-viraemic donors, transmission is only likely to occur with liver transplants	Yes
HCV infection (hepatitis C virus)	Worldwide Prevalence > 3 % in many countries of Africa (Egypt > 15 %), genotype 4b, Asia and local regions of other countries worldwide (Europe, e.g. Italy; America; Australia)	Transplantation of organs to recipients with HCV viraemia possible; in all other cases avoid *de novo* infections by prophylactic treatment by direct-acting anti-viral agents (DAAs). Check for latest therapy recommendations. Use donors according to case-based decisions	Yes
Hepatitis D virus infection	Relevant in countries with high HBsAg and HDV prevalence	*De novo* infection of naïve recipients may be lethal. HDV needs HBsAg for replication. Use of donors not recommended	

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Disease (pathogen)	Geographic distribution, endemic zones and risks	Remarks	Transmission reported*
Hepatitis E virus infection	Insanitary water in developing countries (genotype HEV1 and HEV2), zoonosis in developed countries (consumption of undercooked infected meat – genotypes HEV3 and HEV4). Infection can be acquired by food and rarely via the graft	Risk of acquired HEV infection after transplantation requires recipient monitoring (HEV-NAT) and early treatment to prevent rapid progression to liver cirrhosis. In some countries retrospective testing of donors by HEV-NAT is done and it is accepted practice to transplant HEV-viraemic grafts because treatment is possible by Ribavirin	Yes
Herpes virus infections (HSV-1 and 2, VZV, HHV6)	Worldwide	Avoid *de novo* infection of naïve recipients. Frequent reactivation in recipients. Anti-viral prophylaxis is recommended if D+/R–. Donors with successfully treated Herpes encephalitis can be used (see §8.6.2.9)	Yes
Kaposi sarcoma-associated herpes virus/human herpes virus 8 (KSHV/HHV8)	Prevalence in Mediterranean Basin or Africa generally very high	Serology generally unavailable prior to transplant. Consider NAT monitoring if D+/R– (or R+) because of oncogenic potential (e.g. Kaposi sarcoma, lymphoma, Castleman disease) after primary infection or reactivation	Yes
Histoplasmosis (*Histoplasma capsulatum*)	North America (Ohio and Mississippi rivers), Central and South America, Indonesia, Africa	Test immigrants from endemic areas (≈ 20 % of people infected, most asymptomatic) by serology, antigen tests or PCR. In endemic areas, no screening of recipients is done and anti-fungal prophylaxis is recommended only if donors are infected, and is used in naïve recipients or lung transplants. Reactivation or dissemination under immunosuppression in previously infected recipients may occur and may require treatment	Yes
HIV infection (human immunodeficiency virus I/II)	HIV-1: Estimated adult prevalence >1-5 % in sub-Saharan Africa, Russia, Ukraine, Estonia, Thailand, Papua-New Guinea, Belize, Surinam, Guyana, some Caribbean regions; HIV-2: especially western Africa and countries historically linked to this region	Currently donors with HIV disease (or typically HIV seropositive) are not used. Testing should detect HIV-1, HIV-2 and all subtypes. Donors with HIV infection can be used for (HIV-positive) recipients within an experimental protocol	Yes
HTLV-1/2 infection (human T-leukaemia virus 1/2)	HTLV-1: Romania; southern Japan; Melanesia, Middle East, some Chinese provinces; Caribbean (2-5 %); some US states, parts of South America, Africa HTLV-2: intravenous drug abusers in USA, Europe; South America (Brazil); native Americans; south-east Asia (Vietnam)	Screen at-risk donors (migration), their sexual partners and children (maternal vertical transmission). If infection is confirmed, then organs should not be transplanted into an elective naïve recipient	Yes
Human polyomavirus Family	High infection rate worldwide, so most donors are infected	In cases of suspected progressive multifocal leuko-encephalopathy, refer to §8.9; For all other issues refer to §8.6.2.17	Yes
Influenza (influenza viruses)	Worldwide: annual prevalence and subtypes change. Latest national recommendations must be regularly checked	Prophylactic treatment of recipients should be considered. Donors at high risk of viraemia must be carefully evaluated. Check national recommendations for latest updates before further decisions. Specific recommendations cannot be given due to rapid changes in epidemiology and the virus itself	Yes
LCMV infection (lymphocytic choriomeningitis virus)	North and South America, Europe, Australia, Japan	Difficult to establish diagnosis; check for contact with rodents. Donors with acute infections should not be used	Yes

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Disease (pathogen)	Geographic distribution, endemic zones and risks	Remarks	Transmission reported*
Legionellosis (*Legionella* spp.)	Worldwide	Water, air-conditioning, etc.	
Leishmaniasis (cutaneous and visceral) (*Leishmania* spp.)	All countries with certain sand-fly species: all around the Mediterranean Sea, Middle East, Afghanistan, Asia, southern USA, Central and South America, sub-Saharan Africa	No precise exclusion criteria for organ donation described. Universal donor screening is not recommended [259-260, 272, 307]. If donor serology [259] or NAT as sensitive method [307-308] is positive, strict monitoring of the recipient post-transplant is recommended, rather than organ exclusion. Check donors coming from endemic areas since there is delayed breakthrough in visceral (months) and cutaneous (decades) forms. If reactive to serology or antigen test or NAT, or suspected, take biopsy from liver, spleen, intestine and skin lesions. Curative chemotherapy of infected persons possible, but outcome is very poor in visceral form (contraindicative)	
Leptospirosis (*Leptospira* spp.)	Standing water in (sub) tropical areas	Acute infection affects all organs	
Malaria (*Plasmodium* spp.)	Any (sub)tropical country is a risk area. *P. falciparum*: sub-Saharan Africa, Southeast Asia, Indian subcontinent, South America (Amazon Basin), Haiti, Dominican Republic, Oceania; *P. malariae*, *P. ovale*: sub-Saharan Africa; *P. vivax*: Southeast Asia, Indian subcontinent, Brazil (Amazon Basin)	Check travellers and immigrants from endemic countries for infection (symptoms: fever, disseminated intravascular coagulation, multi-organ failure; diagnostics: blood drop, PCR if indicated). Most centres reject parasitaemic donors. Successfully treated and recovered donors may be used, with some exceptions, e.g. liver. Consider prophylactic treatment of recipients	Yes
Microsporidiosis (*Microsporidia* spp.)	Contaminated water	Transmitted via contaminated water. Spore with thick wall in intestine. Contagious and disseminates (brain, kidney). No effective therapy known	
Multi-drug resistant bacteria (e.g. MRSA, VRE, ESBL)	Worldwide: prolonged hospital stays or any stay in nursing homes or exposure to antibiotics	Important risk factor. Check screening on admission to, and during stay at, ICU. Organs without contamination/infection can be used under prophylactic recipient care; all other cases need an individualised decision	Yes
Non-tuberculous mycobacteria infection (non-tuberculous mycobacteria)	Worldwide	Clinical relevance under investigation	
Parvovirus B19 infection (human parvovirus B19)	Worldwide		Yes
South American Blastomycosis (*Paracoccidioides brasiliensis*)	Soil in (sub-)tropical Central and South America (rural areas or working there; especially Brazil [309])	Trimethoprim-sulfamethoxazole prophylaxis for *Pneumocystis jiroveci* pneumonia is 'cross-effective'. In endemic regions, donors with a history of exposure (living in rural area in endemic regions, particularly those working in agricultural occupations) should be screened prior to transplant to rule out asymptomatic paracoccidioidomycosis infections. Diagnostic methods for screening include radiographic studies searching for calcifications (albeit a non-specific finding) in sites such as adrenal glands, prostate, thyroid, lymph nodes, and spleen, along with serology and skin tests. Donors with active disease are not accepted; living donors should be treated before donation	No

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Disease (pathogen)	Geographic distribution, endemic zones and risks	Remarks	Transmission reported*
Pneumocystis pneumonia (*Pneumocystis jirovecii (carinii)*)	Worldwide: infection risk in long-term patients in ICU, immunosuppressed or immunodeficient patients	Partly avoidable problem with specific prophylaxis in recipients. Disseminated infection in donors contraindicated	Yes
Prion disease (prions)	Worldwide	No treatment available. No screening assay. Risk evaluation for CJD/vCJD. Individualised decisions for at-risk donors. Confirmed infection is an absolute contraindication	
Algemia (*Prototheca* spp.)	Worldwide		Yes
Rabies (Rabies virus)	Animal bites or salivary contact (dogs, bats, other mammals: household and wildlife) Worldwide, though some island territories are low-risk (Japan, Taiwan, UK, Iceland, Australia (where other Lyssavirus exist), New Zealand, Norway, Sweden, Finland). No restriction can be provided for specific animal population in a particular country due to the variability of species infected	Transmission lethal unless previously vaccinated. Only NAT of brain tissue after autopsy is confirmative, but not exclusive. History of animal contact (bites) and any kind of current neurologic disorder is suspicious. Long intervals can occur between bites/animal contact and onset of symptoms (months to years). Donors with recent exposure should not be accepted	Yes
Salmonellosis (*Salmonella* non-typhoid spp.)	Food and poor sanitary conditions, warm or (sub) tropical countries		
Scedosporium apiospermum infection (*Scedosporium apiospermum*)	Worldwide in immunocompromised people		Yes
Bilharziosis (*Schistosoma* spp.)	Contaminated water (Africa, Middle East, Japan, China, Caribbean, South America)	Praziquantel is used for treatment in non-transplant conditions. If previous infection is suspected (liver, intestine, urinary tract), based on serological screening testing or clinical signs, urine or faeces should be tested for eggs	Yes [310]
Strongyloidiasis (*Strongyloides* spp.)	Warm areas with poor sanitary conditions: Southeast Asia, sub-Saharan Africa, Central America, Brazil, southern USA, tropical Australia, Spain	Check faeces for larvae (or tracheal secretions if dissemination can be assumed) in donors from (or having travelled to) endemic areas with the known limited sensitivity. Serology is the most useful screening assay. Auto-infection via faeces from the intestines of asymptomatic carriers occurs. Suspect infection if symptoms of gastro-intestinal infection with urticaria, oeosinophilia and Gram-negative meningitis or pulmonary complications exist. Consider empiric ivermectin in recipients of unscreened, at-risk donors. Immunosuppressed patients have a hyper-infective status, which requires pre-emptive treatment by, e.g. ivermectin. Otherwise lethal	Yes
Cysticercosis (*Taenia solium*)	Worldwide. Frequent in underdeveloped countries or in poor sanitary conditions (Asia, Africa, Latin America)	No precise exclusion criteria for organ donation are described. Typical CT/MRI lesions of neurocysticercosis. Inspection of meat and avoidance of raw meat consumption are the best prevention. Contagious only if tapeworm eggs are in the intestine	Yes

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Disease (pathogen)	Geographic distribution, endemic zones and risks	Remarks	Transmission reported*
Tick-borne encephalitis by various viral species	Worldwide. Seasonally and locally endemic (e.g. European and far-Eastern types of encephalitis occur from April to November, below 1 400 m altitude)	Check worldwide: any tick bites, seasonal association with neurologic disorders. Viraemic donors should not be used	Yes [311]
Toxoplasmosis (*Toxoplasma gondii*)	Worldwide (animal contact)	Risk for naïve recipients of muscle tissue (e.g. heart and/or VCAs). Specific prophylaxis mandatory in any recipient	Yes
Trematode species infection *Paragonimus*: lung *Clonorchis*: liver *Fasciola*: liver *Schistosoma*: liver	Middle East, Africa, South America, Caribbean islands, east Asia, or anywhere in waste or water or meat	A risk if skin lesions, travel history and water contact in prevalent countries are all present. In donors from endemic areas or at risk after travelling: check faeces, urine, tracheal secretions, blood (in case of oeosinophilia) for eggs. Schistosoma serology is available for screening donors at risk. Parasites can be treated by specific medication	Yes
Syphilis (*Treponema pallidum*)	Worldwide	Treatment by antibiotics successful	Yes
Sleeping sickness (*Trypanosoma brucei* spp.)	Sub-Saharan Africa, different sub-species	African Sleeping Sickness: different sub-species cause variants with progressive symptoms. Lethal	
Chagas disease (*Trypanosoma cruzi*)	Central and South America (and the Mexican and Latin American immigrant populations of USA)	Check donors from endemic areas (serology, echocardiography, CT of brain for chronic infection, buffy coat from blood in acute infection). No donation from donors with acute infection. The heart and intestine should not be used from donors with chronic infection, while other organs may be used. Recipients having previous contact with the parasite should receive therapy if parasitaemia re-occurs, e.g. benznidazole. Recipients of organs from Chagas-infected donors should be monitored closely for parasitaemia (PCR is the preferred method) and treated as soon as it is detected	Yes [312]
Tuberculosis (*Mycobacterium tuberculosis*)	Worldwide (Asia, Africa, Central and South America, Europe), poor sanitary and/or economic conditions, extra-pulmonal manifestations (Southeast Asia, Middle East)	Therapy in recipients is difficult. Donors with active/disseminated tuberculosis should not be used. It is advisable to initiate pre-transplant prophylaxis (e.g. INH/B6) in recipients for latent TB or transmission risk	Yes
Ureaplasma		When hyperammonaemia is detected in (lung-)recipients, targeted screening for mycoplasma / ureaplasma in BAL (not detected in standard microbiological testing)	Yes
Varicella (*varicella–zoster virus*)	Worldwide	Naïve adults can still become infected by this childhood disease. Anti-viral prophylaxis may reduce the risk of zoster in seropositive recipients (anti-CMV therapy/prophylaxis also active against VZV)	Yes
WNV infection (West Nile virus)	Epidemic breakouts during late summer (Africa, Asia, Middle East, Europe, USA), other Arbo-virus worldwide	Transmission of acute infection often lethal. Screening helpful in regions with reported infections or epidemics within previous 2 weeks. Seasonal retrospective NAT screening in donors (Italy)	Yes
Yellow Fever (Yellow fever virus)	Africa, South America	No specific criteria exist (see §8.6.2.5). Donors with positive NAT test or clinical symptoms compatible with Yellow Fever should be excluded for 28 days from the positive test or the onset of symptoms; or donor with previous history of YF vaccine within the last 28 days.	

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Disease (pathogen)	Geographic distribution, endemic zones and risks	Remarks	Transmission reported*
Zika virus infection (Zika virus)	Outbreaks of primary infection are possible in regions with presence of competent vectors, permissive climate and where there is intense movement of people	The Zika virus (RNA-virus, *Flaviviridae* family) is transmitted mostly by *Aedes aegypti* mosquitoes. Mild illness (e.g. fever, rash, arthralgia or conjunctivitis) with more than 80 % asymptomatic infections may be observed after an incubation period of up to a week, with symptoms resolving after one week. Viraemia may be detected by NAT. Donors with positive NAT test or clinical symptoms compatible with Zika should be excluded for 28 days from the positive test or the onset of symptoms	

* Transmission reported by solid-organ transplantation: Yes = reported, No = not reported, but high probability of transmission without documented cases or where data are lacking for robust conclusions.

Table 8.9. **General considerations for infections and vaccines**

In general	Geographic distribution, considerable risks	Remarks	Transmission reported*
Respiratory tract infection	Worldwide	Problem for lung transplantation	Yes
Urinary tract infection, pyelonephritis	Worldwide in countries with poor sanitary and economic conditions (a problem for living donations)	Results in sepsis if overlooked; generally only a risk for recipients of kidney transplants	Yes
Vaccinations during past 4-6 weeks of the donor by live vaccines	Consider live vaccine in: • Influenza (inhaled = live) • Varicella • Rotavirus • Measles • Mumps • Rubella • BCG • Smallpox • *V. cholera* (oral = live) • Yellow fever • *Salmonella typhi* (oral = live) • Polio (oral = live)	Live vaccines are equivalent to transmission of acute viral infection: individual risk assessment of potential recipient for 28 days after vaccination of the donor. For some vaccines, limitations exist only for specific organs: • Inhaled influenza vaccine – lung, face • Rotavirus – intestine • Cholera – intestine • *Salmonella* – intestine	Yes
Vaccinations during past 4-6 weeks of the donor by inactivated vaccines or passive immunisation	Consider inactivated vaccine in: • Influenza (injectable = inactivated) • *V. cholera* (injectable = inactivated) • *Salmonella typhi* (injectable = inactivated) • Polio (injectable = inactivated)	Other vaccines or passive immunisation of donors may not harm the recipient, but may confound diagnostic	No
	For SARS-CoV-2 vaccine see §8.2.4		

* Transmission reported by solid-organ transplantation: Yes = reported, No = not reported.

8.12. Vigilance methods and tracking

Extensive communication, in both directions between the OPO and the transplant centres, before, during and after transplantation, is crucial [1, 4]. If a recipient develops any unexpected signs and/or symptoms, including unexplained fever, leukocytosis, altered mental status or other signs of hidden infection [2, 313], or if donor-derived disease is suspected, screening of all other graft recipients should be carried out to detect a donor-to-recipient infection and facilitate early initiation of therapy [1, 313]. Any documented infection early post-transplant should also warrant careful review of donor cultures and consideration of the donor as the potential source. Some donor-derived infections may become apparent up to several months after the transplant, and suspicion of imputability requires a high index of suspicion (e.g. HHV8).

It is mandatory for the health authority of each EU member state, and strongly recommended to Council of Europe member states, to establish a national vigilance system for monitoring serious adverse reactions and events of transplantation (see Chapter 16). Free and rapid exchange of data between the vigilance systems of all member states must occur in order to facilitate safe international organ exchange.

Especially in the case of assumed or confirmed post-transplant infections, the exchange of proper and correct information must be done without delay to ensure that proper diagnostics, preventive and therapeutic interventions (if indicated) are put in place for other recipients.

8.13. Preventive strategies in organ recipients

Preventive strategies that can minimise the risk of donor-derived diseases among potential recipients include:

a. For some infectious diseases, recipient vaccination may reduce the risk of disease transmission by a graft. Therefore, patients at risk of end-stage organ failure should complete their vaccination programme as early as possible. This should include vaccination against hepatitis A, hepatitis B, diphtheria, tetanus, pertussis, *S. pneumonia* and influenza, as well as prior exposure to immunosuppression, measles, mumps, rubella and varicella [26-27, 153, 314]. Their clinical response to vaccination, and antibody status thereafter, should be monitored and, if required, vaccination should be repeated. It is important to check the complete vaccination history of a recipient prior to transplantation [315].

b. Recipient vaccination should be checked and completed as recommended, and extended to the relevant infections prevalent if travel or contact with persons from foreign countries exists or is planned [316], and may also be necessary due to local endemic or pandemic diseases.

c. Prophylactic vaccination may not be effective for some end-stage organ diseases [315].

d. Treatments with antibiotic, anti-viral and/or anti-parasitic prophylaxis during transplantation vary from centre to centre for CMV, *Toxoplasmosis*, HSV, VZV and *Pneumocystis jiroveci* (*carinii*) etc. These protocols should be updated to mitigate against expected transmissible infections. After transplantation, close and regular follow-up of recipients helps to rule out infections. This includes screening for latent viruses. Chemoprophylaxis with (val) ganciclovir may mitigate the complications of EBV infection (PTLD) in paediatric D+/R– recipients [317]. Such strategies should be evaluated for improved effectiveness.

e. An antibody response to an infection acquired through the transplanted organ may not develop [218]. It is recommended that clinicians rely on NAT or other direct pathogen-detecting assays (e.g. HBsAg) to screen organ recipients for transmitted infections [1, 27]. Because late manifestation of latent infections, e.g. CMV, may occur in recipients, long-term follow-up should include targeted screening for such risks.

f. Pan-genotypic hepatitis C treatment by new DAAs allows treatment before transplantation or after transplantation with the risk associated with interaction with immunosuppressive drugs (see Appendix 16).

g. Recipient testing after transplantation should be done at a minimum as outlined in Table 8.4 (see section 8.2).

h. Recipients should be informed about the risks associated with not receiving an organ versus the risks of receiving an organ from a donor with increased risk for infections. [49]

8.14. Conclusion

This chapter provides an overview of infectious disease transmission risks. The chapter does not repeat basics in the care of ICU patients for infection prevention, diagnostics and treatment, which are part of best practice in standard intensive care medicine. Although the contents are up to date for most of the important pathogens causing problems in transmission risks, it is impossible to cover all pathogens that may exist. New advances in therapy as well as newly emerging pathogens require the user to collaborate closely with transplant infectious disease experts. Whenever in doubt, before discarding a donor or an organ, it is best practice to discuss the issue with transplant infectious disease experts for final decisions. Internationally when reviewing literature and guidelines a global consensus exists for most questions, and independent research comes to equivalent solutions. Therefore, the experts working on this chapter decided to keep discussions here as short as possible.

Research agenda

From the literature and discussion of the available evidence, several topics have been identified for which evidence is inconsistent, insufficient or non-existent. The authors of this guide recommend that future research should focus on the following research gaps:

1 Monitoring for new pathogens, their associated donor-derived disease-transmission risks and their impact on organ viability (e.g. SARS-CoV-2).
2 Monitoring the associated donor-derived disease-transmission risks of known pathogens.
3 Monitoring changes in vectors responsible for geographic spread of emerging pathogens.
4 Trends in multidrug-resistant bacteria and their associated donor-derived disease-transmission risks.
5 Changes in treatment options for HIV, HBV, HCV and HEV, with the implications for associated donor-derived disease-transmission risks.

8.15. References

1. Ison MG, Nalesnik MA. An update on donor-derived disease transmission in organ transplantation. *Am J Transplant* 2011;11:1123-30.
2. Ison MG, Grossi P and the AST Infectious Diseases Community of Practice. Donor-derived infections in solid organ transplantation. *Am J Transplant* 2013; 13(Suppl 4):22-30.
3. Kaul D, Vece G, Blumberg E *et al.* Ten years of donor-derived disease: A report of the disease transmission advisory committee. *Am J Transplant* 2021; 21(2):689-702. https://doi.org/10.1111/ajt.16178 [online publication 25 July 2020].
4. Fishman JA, Greenwald MA, Grossi PA. Transmission of infection with human allografts: essential considerations in donor screening. *Clin Infect Dis* 2012;55:720-7.
5. Fischer-Fröhlich CL, Lauchart W, Patrzalek D. Evaluation of infectious disease transmission during organ donation and transplantation: viewpoint of a procurement co-ordinator. *Organs Tiss Cells* 2009;12:35-54.
6. Fischer SA, Lu K and the AST Infectious Diseases Community of Practice. Screening of donor and recipients in solid organ transplantation. *Am J Transplant* 2013;13(Suppl 4):9-21.
7. Len O, Los-Arcos I, Aguado JM *et al*; Grupo de Estudio de la Infección en el Trasplante (GESITRA) of the Sociedad Española de Enfermedades Infecciosas y Microbiología Clínica (SEIMC) and the Organización Nacional de Trasplantes (ONT). Selection criteria of solid organ donors in relation to infectious diseases: a Spanish consensus. *Transplant Rev (Orlando)* 2020:34: 100528. https://doi.org/10.1016/j.trre.2020.100528.
8. Sarmento A, Freitas F, Tavares AP. Viral screening in the donation/transplant process in Portugal: state-of-the-art in 2002. *Organs and Tissues* 2003;6(1):23-30.
9. Depoortere E, Coulombier D, ECDC Chikungunya Risk Assessment Group. Chikungunya risk assessment for Europe: recommendations for action. *Euro Surveillance* 2006;11:E060511.2. https://doi.org/10.2807/esw.11.19.02956-en.
10. Nanni Costa A, Grossi P, Porta E *et al.* Measures taken to reduce the risk of West Nile virus transmission by transplantation in Italy. *Euro Surveillance* 2008;13(42): pii=19009.
11. López-Medrano F, Cordero E, Gavaldá J *et al.* Management of influenza infection in solid-organ transplant recipients: consensus statement of the Group for the Study of Infection in Transplant Recipients (GESITRA) of the Spanish Society of Infectious Diseases and Clinical Microbiology (SEIMC) and the Spanish Network for Research in Infectious Diseases (REIPI). *Enferm Infecc Microbiol Clin* 2013;31:526.e1-20.
12. Kumar D, Morris MI, Kotton CN *et al.* Guidance on novel influenza A/H1N1 in solid organ transplant recipients. *Am J Transplant* 2010;10:18-25.
13. Danziger-Isakov LA, Husain S, Mooney ML *et al*; ISHLT Infectious Diseases Council. The novel 2009 H1N1 influenza virus pandemic: unique considerations for programs in cardiothoracic transplantation. *J Heart Lung Transplant* 2009;28(12):1341-1447.
14. Thwaites GE, Day NP. Approach to fever in the returning traveler. *N Engl J Med* 2017 Feb 9;376(6):548-60.
15. European Centre for Disease Prevention and Control: Website 2020. Results of search for infectious diseases restricted on Coronavirus and COVID-19, at www.ecdc.europa.eu/en/search?f%5B0%5D=diseases%3A2942&f%5B1%5D=diseases%3A2943 and results of search for COVID-19 pandemic, at www.ecdc.europa.eu/en/covid-19-pandemic (last accessed 18 August 2020).
16. World Health Organization: Website. Results of search for Coronavirus disease (COVID-19) pandemic, at www.who.int/emergencies/diseases/novel-coronavirus-2019 (last accessed 18 August 2020).
17. Suryaprasad A, Basavaraju SV, Hocevar SN *et al.* Transmission of hepatitis C virus from organ donors despite nucleic acid test screening. *Am J Transplant* 2015;15:1827-35.
18. Annambhotla PD, Gurbaxani BM, Kuehnert MJ, Basavaraju SV. A model to estimate the probability of human immunodeficiency virus and hepatitis C infection despite negative nucleic acid testing among increased-risk organ donors. *Transpl Infect Dis* 2017; 19(2). https://doi.org/10.1111/tid.
19. Pondrom S. Can transplantation be zero risk? *Am J Transplant* 2012;12:509-10.
20. Mezochow AK, Henry R, Blumberg EA, Kotton CN. Transfusion transmitted infections in solid organ transplantation. *Am J Transplant* 2015;15:547-54.

21. Brennan MB, Herwaldt BL, Kazmierczak JJ *et al.* Transmission of Babesia microti parasites by solid organ transplantation. *Emerg Infect Dis* 2016;22(11): 1869-76. https://doi.org/10.3201/eid2211.151028.
22. Kaul DR, Taranto S, Alexander C *et al.* Donor screening for human T-cell lymphotrophic virus 1/2: changing paradigms for changing testing. *Am J Transplant* 2010;10:207-13.
23. Scharz P, Custódio G, Rheinheimer J *et al.* Brain death-induced inflammatory activity is similar to sepsis-induced cytokine release. *Cell Transplantation* 2018;27:1417-24.
24. Centers for Disease Control and Prevention. HIV transmitted from a living organ donor – New York City, 2009. *Morb Mortal Wkly Rep* 2011;60(10):297-301.
25. Blumberg EA, Ison MG, Pruett TL *et al.* on behalf of the Optimal Testing of the Live Organ Donor Consensus Conference participants. Optimal testing of the live organ donor for blood-borne viral pathogens: the report of a consensus conference. *Am J Transplant* 2013;13:1405-15.
26. Len O, Garzoni C, Lumbreras C *et al.* on behalf of the ESCMID Study Group of Infection in Compromised Hosts (ESGICH). Recommendations for screening of donor and recipient prior to solid organ transplantation and to minimize transmission of donor-derived infections. *Clin Microbiol Infect* 2014;20(Suppl 7):10-18.
27. Jones JM, Kracalik I, Levi ME *et al.* Assessing solid organ donors and monitoring transplant recipients for human immunodeficiency virus, hepatitis B virus, and hepatitis C virus infection – U.S. Public Health Service Guideline, 2020. *Morb Mortal Wkly Rep*, Recomm. Rep. 2020 Jun 26;69(4):1-16. https://doi.org/10.15585/mmwr.rr6904a1.
28. Chevaliez S, Feld J, Cheng K *et al.* Clinical utility of HCV core antigen detection and quantification in the diagnosis and management of patients with chronic hepatitis C receiving an all-oral, interferon-free regimen. *Antivir Ther* 2018;23(3):211-17.
29. Koutsoudakis G, Pérez-del-Pulgar S, Forns X. Occult hepatitis C virus infection: are we digging too deep? *Gastroenterology* 2017;152:472-81.
30. Gambato M, Pérez-del-Pulgar S, Hedskog C *et al.* Hepatitis C virus RNA persists in liver explants of most patients awaiting liver transplantation treated with an interferon-free regimen. *Gastroenterology* 2016;151:633-6.
31. Levitsky J, Formica RN, Bloom RD *et al.* The American Society of Transplantation Consensus Conference on the Use of Hepatitis C Viremic Donors in Solid Organ Transplantation. *Am J Transplant* 2017 Nov;17(11):2790-2802. https://doi.org/10.1111/ajt.14381 [epub 1 July 2017].
32. Selzner N, Berenguer M. Should organs from hepatitis C positive donors be used in hepatitis C negative recipients for liver transplantation? *Liver Transplant* 2018;24:831-40.
33. Scott N, Snell G, Westall G *et al.* Cost-effectiveness of transplanting lungs and kidneys from donors with potential hepatitis C exposure and infection. *Nature* 2020;10:1459. https://doi.org/10.1038/s41598-020-58215-z.
34. Goldberg D, Abt PL, Blumberg EA *et al.* Trial of transplantation of HCV-infected kidneys into uninfected recipients. *N Engl J Med* 2017;376(24):2394-5. https://doi.org/10.1056.NEJMc1705221.
35. Woolley AE, Singh SK, Goldberg HJ *et al.* Heart and lung transplants from HCV-infected donors to uninfected recipients. *N Engl J Med* 2019;380(17):1606-17. https://doi.org/10.1056/NEJMoa1812406.
36. Schnegg B, Bart N, Dharan NJ *et al.* Heart transplantation from hepatitis C-positive donors in the era of direct acting antiviral therapy: a comprehensive literature review. *Transplant Direct* 2019;5(9):e486. https://doi.org/10.1097/TXD.0000000000000928.
37. Luckett K, Kaiser TE, Bari K *et al.* Use of hepatitis C virus antibody-positive donor livers in hepatitis C nonviremic liver transplant recipients. *J Am Coll Surg* 2019;228(4):560-7. https://doi.org/10.1016/j.jamcollsurg.2018.12.004.
38. Cotter TG, Paul S, Sandıkçı B *et al.* Increasing utilization and excellent initial outcomes following liver transplant of hepatitis C virus (HCV)-viremic donors into HCV-negative recipients: outcomes following liver transplant of HCV-viremic donors. *Hepatology* 2019;69(6):2381-95.
39. Cotter TG, Aronsohn A, Reddy KG, Charlton M. Liver transplantation of HCV-viremic donors into HCV-negative recipients in the USA: increasing frequency with profound geographic variation. *Transplantation* 2021 Jun 1:105(6):1285-90. https://doi.org/10.1097/TP.0000000000003382 [online publication 29 June 2020].
40. Polanco NP, Goldberg D. Transplanting livers from 'HCV-positive' donors to HCV-negative recipients: increased experience but many unanswered questions. *Am J Gastroenterol* 2020;115(7):1022-3. https://doi.org/10.14309/ajg.0000000000000649.
41. McPherson S, Elsharkawy AM, Ankcorn M *et al.* Summary of the British Transplantation Society UK guidelines for hepatitis E and solid organ transplantation. *Transplantation* 2018;102:15-20.
42. [Anon.] HIV transmitted from a living organ donor – New York City, 2009. *Am J Transplant* 2011;11(6):1334-7. https://doi.org/10.1111/j.1600-6143.2011.03631.x.
43. Lal H, Cunningham AL, Godeaux O *et al.* Efficacy of an adjuvanted herpes zoster subunit vaccine in older adults. *N Engl J Med* 2015 May 28;372(22):2087-96.

44. European Centre for Disease Prevention and Control. Stockholm, Sweden: Annual epidemiological reports, available at https://ecdc.europa.eu/en/annual-epidemiological-reports, and Disease surveillance reports, available at www.ecdc.europa.eu/en/surveillance-and-disease-data/disease-surveillance-reports, last accessed 17 August 2020.
45. Kucirka LM, Sarathy H, Govindan P *et al.* Risk of window period hepatitis C infection in highly infectious risk donors: systematic review and meta-analysis. *Am J Transplant* 2011;11:1188-1200.
46. Council of Europe, European Directorate for the Quality of Medicine & HealthCare (EDQM). *Risk behaviours having an impact on blood donor management. Technical Memorandum TS057.* Strasbourg: EDQM, 2011.
47. White S, Rawlinson W, Boan P *et al.* Infectious disease transmission in solid organ transplantation: donor evaluation, recipient risk, and outcomes of transmission. *Transplantation Direct* 2018;4:e416; https://doi.org/10.1097/TXD.0000000000000852.
48. Davion K, Ushiro-Lumb I, Lawrence M *et al.* Infections and associated behaviors among deceased organ donors: informing the assessment risk. *Transplant Inf Dis* 2019;21:e13055. https://doi.org/10.1111/tid.13055.
49. OPTN (Organ Procurement and Transplantation Network)/UNOS Disease Transmission Advisory Committee. Guidance on explaining risk related to the use of U.S. PHS increased risk donor organs when considering organ offers. DTAC/OPTN/UNOS, 2017, available at https://optn.transplant.hrsa.gov/media/2116/guidance_increased_risk_organ_offers_20170327.pdf, accessed 20 August 2020.
50. SaBTO: Advisory Committee on the Safety of Blood, Tissues and Organs (SaBTO). Microbiological safety guidelines (previously known as guidance on the microbiological safety of human organs, tissues and cells in transplantation), Version 2.0, revised March 2020. SaBTO Secretary, United Kingdom Department of Health, London, 2011, available at https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/876161/SaBTO-microbiological-safety-guidelines.pdf, accessed 20 August 2020.
51. OPTN (Organ Procurement and Transplantation Network), ed. Disease Transmission Advisory Committee, October 2018 proceedings, Chicago IL 2018, available at https://optn.transplant.hrsa.gov/media/2746/20181016_dtac_meeting_minutes.pdf, accessed 1 February 2021.
52. OPTN (Organ Procurement and Transplantation Network), ed. Disease Transmission Advisory Committee, March 2019 meeting, Chicago IL 2019, available at https://optn.transplant.hrsa.gov/media/2936/20190318_dtac_minutes.pdf, accessed 1 February 2021.
53. Cooper B, Medley G, Bradley S *et al.* An augmented data method for the analysis of nosocomial infection data. *Am J Epidemiol* 2008;168:548-57.
54. Witte W, Strommenger B, Klare I *et al.* Bakterielle Erreger von Krankenhausinfektionen mit besonderen Resistenzen und Multiresistenzen: Teil 1, Diagnostik und Typisierung. *Bundesgesundheitsblatt – Gesundheitsforsch – Gesundheitsschutz* 2004;47:352-62 (in German).
55. Witte W, Strommenger B, Klare I *et al.* Bakterielle Erreger von Krankenhausinfektionen mit besonderen Resistenzen und Multiresistenzen: Teil 2, Erfassung und Bewertung gem. §23 Abs.1IfSG in einem regionalen Netzwerk. *Bundesgesundheitsblatt – Gesundheitsforsch – Gesundheitsschutz* 2004;47:363-8 (in German).
56. Agence de la biomédicine. *Prévention de la transmission de bactéries et d'agents fongiques aux receveurs d'organes.* Version longue, 2008 (in French), available at www.infectiologie.com/UserFiles/File/medias/_documents/consensus/recommandations_biomedecinefongique_long.pdf, accessed 20 August 2020; or the short version at www.agence-biomedecine.fr/IMG/pdf/prevention-de-la-transmission-de-bacteries-et-d-agents-fongiques-aux-receveurs-d-organes-texte-court.pdf.
57. Agence de la biomédecine. Prévention de la transmission de bactéries et d'agents fongiques aux receveurs d'organes. *Med Mal Inf* 2009;39:682-97.
58. Singh G, Hsia-Lin A, Skiest D *et al.* Successful kidney transplantation from a hepatitis B surface antigen-positive donor to an antigen-negative recipient using a novel vaccination regimen. *Am J Kidney Dis* 2013;61:608-11.
59. Len O, Gavaldà J, Blanes M *et al.* Donor infection and transmission to the recipient of a solid allograft. *Am J Transplant* 2008;8:2420-5.
60. Caballero F, López-Navidad A, Perea M *et al.* Successful liver and kidney transplantation from cadaveric donors with left sided bacterial endocarditis. *Am J Transplant* 2005;5:781-7.
61. Ruiz I, Gavaldà J, Monforte V. Donor-to-host transmission of bacterial and fungal infections in lung transplantation. *Am J Transplant* 2006;6:178-82.
62. ECDC (European Centre for Disease Prevention and Control). Carbapenemase-producing bacteria in Europe. Stockholm: ECDC, 2013, available at www.ecdc.europa.eu/en/publications-data/carbapenemase-producing-bacteria-europe, accessed 20 August 2020.
63. Mathers AJ, Cox HL, Bonatti H *et al.* Fatal cross

infection by carbapenem-resistant Klebsiella in two liver transplant recipients. *Transpl Infect Dis* 2009;11: 257-65.

64. Bergamasco MD, Barroso Barbosa M, de Oliveira Garcia D *et al.* Infection with Klebsiella pneumoniae carbapenemase (KPC)-producing K. pneumoniae in solid organ transplantation. *Transpl Infect Dis* 2012; 14:198-205.
65. Wu TJ, Lee CF, Chou HS *et al.* Suspect the donor with potential infection in the adult deceased donor liver transplantation. *Transplant Proc* 2008;40:2486-8.
66. Martins N, Martins IS, de Freitas WV *et al.* Severe infection in a lung transplant recipient caused by donor-transmitted carbapenem-resistant Acinetobacter baumannii. *Transpl Infect Dis* 2012;14:316-20.
67. Mularoni A, Bertani A, Vizzini G *et al.* Outcome of transplantation using organs from donors infected or colonized with carbapenem-resistant Gram-negative bacteria. *Am J Transplant* 2015 Oct;15(10):2674-82.
68. van Duin D, Bonomo RA. Ceftazidime/avibactam and ceftolozane/tazobactam: second-generation β-lactam/β-lactamase inhibitor combinations. *Clin Infect Dis* 2016 Jul 15;63(2):234-41.
69. Santoro-Lopes G, Subramanian AK, Molina I *et al.* Tuberculosis recommendations for solid organ transplant recipients and donors. *Transplantation* 2018;102(2S Suppl 2):S60-S65. https://doi.org/10.1097/TP.0000000000002014.
70. Bumbacea D, Arend SM, Eyuboglu F *et al.* The risk of tuberculosis in transplant candidates and recipients. *Eur Respir J* 2012;40;990-1013.
71. Morris MI, Daly JS, Blumberg E *et al.* Diagnosis and management of tuberculosis in transplant donors: a donor-derived infections consensus conference report. *Am J Transplant* 2012;12;2288-300.
72. Pinazo MJ, Miranda B, Rodríguez-Villar C *et al.* Recommendations for management of Chagas diseases in organ and hematopoietic tissue transplantation programs in non-endemic areas. *Transplant Rev* 2011;25: 91-101.
73. Aguado JM, Torre-Cisneros J, Fortún J *et al.* Tuberculosis in solid-organ transplant recipient: consensus statement of the Group for study of infection in transplant recipients (GESITRA) of the Spanish Society of Infectious Diseases and Clinical Mircrobiology. *Clin Infect Dis* 2009;48:1276-84.
74. Schmidt T, Schub D, Wolf M *et al.* Comparative analysis of assays for detection of cell-mediated imunity towards cytomegalovirus and M. tuberculosis in sample from deceased organ donors. *Am J Transplant* 2014;14:2159-67.
75. Theodoropoulos N, Jaramillo A, Penugonda S *et al.* Improving syphilis screening in deceased organ donors. *Transplantation* 2015;99:438-43.
76. Roberts SC, Bharat A, Kurihara C *et al.* Impact of screening and treatment of ureaplasma species on hyperammonemia syndrome in lung transplant recipients: a single center experience. *Clin Infect Dis* 2021 Nov 2;73(9):e2531-7. https://doi.org/10.1093/cid/ciaa1570.
77. Fernandez R, Ratliff A, Crabb D *et al.* Ureaplasma transmitted from donor lungs is pathogenic after lung transplantation. *Ann Thorac Surg* 2017 Feb;103(2): 670-1. https://doi.org/10.1016/j.athoracsur.2016.09.026. PubMed PMID: 28109354.
78. Wang X, Greenwood-Quaintance KE, Karau MJ *et al.* Ureaplasma parvum causes hyperammonemia in a pharmacologically immunocompromised murine model. *Eur J Clin Microbiol Infect Dis* 2017 Mar;36(3): 517-22. https://doi.org/10.1007/s10096-0162827-1 [epub 28 Oct 2016]. PubMed PMID: 27796644; PubMed Central PMCID: PMC5310980.
79. Wang X, Karau MJ, Greenwood-Quaintance KE *et al.* Ureaplasma urealyticum causes hyperammonemia in an experimental immunocompromised murine model. *PLoS One* 2016 Aug 18;11(8):e0161214. https://doi.org/10.1371/journal.pone.0161214. eCollection 2016. PubMed PMID: 27537683; PubMed Central PMCID: PMC4990232.
80. Bharat A, Cunningham SA, Scott Budinger GR *et al.* Disseminated ureaplasma infection as a cause of fatal hyperammonemia in humans. *Sci Transl Med* 2015 Apr 22;7(284):284re3. https://doi.org/10.1126/scitranslmed.aaa8419. PubMed PMID: 25904745; PubMed Central PMCID: PMC4677674.
81. Gabardi S, Kubiak D, Chandraker A *et al.* Invasive fungal infections and antifungal therapies in solid organ transplant recipients. *Transpl Int* 2007;20: 963-1015.
82. Huprikar S, Shoham S, the AST Infectious Diseases Community of Practice. Emerging fungal infections in solid organ transplantation. *Am J Transplant* 2013; 13(Suppl 4):262-71.
83. Miller R, Assi M, the AST Infectious Diseases Community of Practice. Endemic fungal infections in solid organ transplantation. *Am J Transplant* 2013;13(Suppl 4):250-61.
84. Azar MM, Turbett SE, Fishman JA, Pierce VM. Donor-derived transmission of Candida auris during lung transplantation. *Clin Infect Dis* 2017 Sep 15;65(6): 1040-2. https://doi.org/10.1093/cid/cix460.
85. Martin SI, Fishman JA, the AST Infectious Diseases Community of Practice. Pneumocystis pneumonia in solid organ transplantation. *Am J Transplant* 2013; 13(Suppl 4):272-9.
86. Singh N, Huprikar S, Burdette SD *et al;* American Society of Transplantation, Infectious Diseases Community of Practice, Donor-Derived Fungal Infection

Working Group. Donor-derived fungal infections in organ transplant recipients: guidelines of the American Society of Transplantation, infectious diseases community of practice. *Am J Transplant* 2012;12(9): 2414-28.

87. Levesque E, Paugam-Burtz C, Saliba F *et al.* Fungal complications after Candida preservation fluid contamination in liver transplant recipients. *Transpl Int* 2015;82:1308-16. https://doi.org/10.1111/tri.12633.
88. Dębska-Ślizien D, Chrobak Ł, Bzoma B *et al.* Candida arteritis in kidney transplant recipients: case report and review of the literature. *Transpl Infect Dis* 2015 Jun:17(3):449-455. https://doi.org/10.1111/tid.12388.
89. *Organización Nacional de Trasplantes* (ONT) ed. Consensus Document of the *Grupo de Estudio de la Infección en el Trasplante* (GESITRA) of the *Sociedad Española de Enfermedades Infecciosas y Microbiología Clínica* (SEIMC) and the *Organización Nacional de Trasplantes* (ONT) on the selection criteria of donors of solid organs in relation to infectious diseases. Madrid, Spain: ONT, 2019.
90. ECDC (European Centre for Disease Prevention and Control). Mosquito maps. ECDC, 2020, available at www.ecdc.europa.eu/en/disease-vectors/surveillance-and-disease-data/mosquito-maps, accessed 18 August 2020.
91. Dalla Gasperina D, Balsamo ML, Garavaglia SD *et al.* Chikungunya infection in a human immunodeficiency virus-infected kidney transplant recipient returning to Italy from the Dominican Republic. *Transpl Infect Dis* 2015 Dec;17(6):876-9.
92. Couderc T, Gangneux N, Chrétien F *et al.* Chikungunya virus infection of corneal grafts. *J Infect Dis* 2012 Sep 15;206(6):851-9.
93. Long KM, Heise MT. Chikungunya virus transmission – more than meets the eye. *J Infect Dis* 2012 Sep 15;206(6):806-7.
94. ECDC (European Centre for Disease Prevention and Control). Dengue outbreak in Madeira, Portugal, March 2013. Stockholm: ECDC, 2014.
95. ECDC (European Centre for Disease Prevention and Control). Rapid risk assessment: Autochthonous cases of dengue in Spain and France. ECDC, 2019, available at www.ecdc.europa.eu/en/publications-data/rapid-risk-assessment-autochthonous-cases-dengue-spain-and-france, accessed 18 August 2020.
96. Simmons C, Farrar J, van Vinh N *et al.* Dengue. *N Engl J Med* 2012;366:1423-32.
97. Tan FL, Loh DL, Prabhakaran K *et al.* Dengue haemorrhagic fever after living donor renal transplantation. *Nephrol Dial Transplant* 2005;20:447-8.
98. Saigal S, Choudhary NS, Saraf N *et al.* Transmission of dengue virus from a donor to a recipient after living donor liver transplantation. *Liver Transplant* 2013;19: 1413-14.
99. Gupta RK, Gupta G, Chorasiya VK *et al.* Dengue virus transmission from living donor to recipient in liver transplantation: a case report. *J Clin Exp Hepatol* 2016 Mar;6(1):59-61.
100. Rosso F, Pineda JC, Sanz AM *et al.* Transmission of dengue virus from deceased donors to solid organ transplant recipients: case report and literature review. *Braz J Infect Dis* 2018 Jan-Feb;22(1):63-9.
101. Morelli MC, Sambri V, Grazi GL *et al.* Absence of neuroinvasive disease in a liver transplant recipient who acquired West Nile virus (WNV) infection from the organ donor and who received WNV antibodies prophylactically. *Clin Infect Dis* 2010;51:e34-e37.
102. Costa AN, Capobianchi MR, Ippolito G *et al.* West Nile virus: the Italian national transplant network reaction to an alert in the north-eastern region, Italy 2011. *Euro Surveillance* 2011;16:41-89.
103. Centers for Disease Control and Prevention. West Nile virus infections in organ transplant recipients – New York and Pennsylvania, August-September, 2005. *Morb Mortal Wkly Rep* 2005;54:1-3.
104. Centers for Disease Control and Prevention. West Nile virus transmission via organ transplantation and blood transfusion – Louisiana, 2008. *Morb Mortal Wkly Rep* 2009;58:1263-7.
105. Iwamoto M, Jernigan DB, Guasch A *et al.* Transmission of West Nile virus from an organ donor to four transplant recipients. *N Engl J Med* 2003;348:2196-203.
106. Lanteri MC, Lee TH, Wen L *et al.* West Nile virus nucleic acid persistence in whole blood months after clearance in plasma: implication for transfusion and transplantation safety. *Transfusion* 2014;54:3232-41.
107. Singh N, Levi ME, AST Infectious Diseases Community of Practice. Arenavirus and West Nile virus in solid organ transplantation. *Am J Transplant* 2013; 13(Suppl 4):361-71. https://doi.org/10.1111/ajt.12128.
108. Winston DJ, Vikram HR, Rabe IB *et al;* West Nile Virus Transplant-Associated Transmission Investigation Team. Donor-derived West Nile virus infection in solid organ transplant recipients: report of four additional cases and review of clinical, diagnostic, and therapeutic features. *Transplantation* 2014;97:881-9.
109. Petersen LR, Brault AC, Nasci RS. West Nile virus: review of the literature. *JAMA* 2013;310:308-15.
110. Komar N, Langevin S, Hinten S *et al.* Experimental infection of North American birds with the New York 1999 strain of West Nile virus. *Emerg Infect Dis* 2003; 9:311-22.
111. Tonry JH, Brown CB, Cropp CB *et al.* West Nile virus detection in urine. *Emerg Infect Dis* 2005;11:1294-6.
112. Murray K, Walker C, Herrington E *et al.* Persistent

infection with West Nile virus years after initial infection. *J Infect Dis* 2010;201:2-4.

113. Barzon L, Pacenti M, Franchin E *et al.* Excretion of West Nile virus in urine during acute infection. *J Infect Dis* 2013;208:1086-92.

114. Levi ME, Kumar D, Green M *et al*; AST Infectious Diseases Community of Practice. Considerations for screening live kidney donors for endemic infections: a viewpoint on the UNOS policy. *Am J Transplant* 2014; 14:1003-11.

115. Cadar D, Maier P, Müller S *et al.* Blood donor screening for West Nile virus (WNV) revealed acute Usutu virus (USUV) infection, Germany, September 2016. *Eurosurveillance* 2017;22(14): pii=30501. https://doi.org/10.2807/1560-7917.ES.2017.22.14.30501.

116. Domanović D, Gossner CM, Lieshout-Krikke R *et al.* West Nile and Usutu virus infections and challenges to blood safety in the European Union. *Emerg Infect Dis* 2019;25(6):1050-7. https://doi.org/10.3201/eid2506.181755.

117. Gourinat AC, O'Connor O, Calvez E *et al.* Detection of Zika virus in urine. *Emerg Infect Dis* 2015:21(1):84-6. https://doi.org/10.3201/eid2101.140894.

118. Nogueira ML, Estofolete CF, Terzian AC *et al.* Zika virus infection and solid organ transplantation: a new challenge. *Am J Transplant* 2017 Mar;17(3):791-5.

119. Barjas-Castro ML, Angerami RN, Cunha MS *et al.* Probable transfusion-transmitted Zika virus in Brazil. *Transfusion* 2016 Jul;56(7):1684-8.

120. Pierrotti LC, Duarte-Neto AN, Song ATW *et al.* Fatal Yellow Fever in a kidney transplant patient. *Clin Infect Dis* 2020;70(1):144-8. https://doi.org/10.1093/cid/ciz389.

121. Grossi PA. Urban spread of flaviviruses: a new challenge in solid-organ transplant recipients. *Clin Infect Dis* 2020;70(1):149-51. https://doi.org/10.1093/cid/ciz390.

122. Nassar E da S, Chamelet ELB, Coimbra TLM *et al.* Jungle yellow fever: clinical and laboratorial studies emphasizing viremia on a human case. *Rev Inst Med Trop São Paulo* 1995 Aug;37(4):337-41.

123. Reusken CBEM, Knoester M, GeurtsvanKessel C *et al.* Urine as sample type for molecular diagnosis of natural Yellow Fever virus infections. *J Clin Microbiol* 2017;55(11):3294-6.

124. CDC (Centers for Disease Control and Prevention). Fatal yellow fever in a traveller returning from Amazonas, Brazil, 2002. MMWR *Morb Mortal Wkly Rep* 2002 Apr 19;51(15):324-5.

125. ECDC (European Centre for Disease Prevention and Control). Yellow fever – Annual epidemiological report for 2017. Stockholm: ECDC, 2017, available at www.ecdc.europa.eu/en/publications-data/yellow-fever-annual-epidemiological-report-2017, accessed 20 August 2020.

126. Kotton CN, Kumar D, Caliendo AM *et al.* The Third International Consensus Guidelines on the Management of Cytomegalovirus in solid-organ transplantation. *Transplantation* 2018 Jun;102(6): 900-31.

127. Razonable RR, Humar A. Cytomegalovirus in solid organ transplant recipients – Guidelines of the American Society of Transplantation Infectious Diseases Community of Practice. *Clin Transplant* 2019 Sep; 33(9):e13512.

128. Allen UD, Preiksaitis JK, AST Infectious Diseases Community of Practice. Post-transplant lymphoproliferative disorders, Epstein-Barr virus infection, and disease in solid organ transplantation: Guidelines from the American Society of Transplantation Infectious Diseases Community of Practice. *Clin Transplant* 2019 Sep;33(9):e13652.

129. Gottschalk S, Rooney CM. Adoptive T-cell immunotherapy. *Curr Top Microbiol Immunol* 2015;391:427-54.

130. Tzannou I, Papadopoulou A, Naik S *et al.* Off-the-shelf virus-specific T cells to treat BK virus, human herpesvirus 6, Cytomegalovirus, Epstein-Barr virus, and Adenovirus infections after allogeneic hematopoietic stem-cell transplantation. *J Clin Oncol* 2017 Nov 1;35(31):3547-57.

131. Regamey N, Tamm M, Wernli M *et al.* Transmission of human herpes virus 8 infection from renal-transplant donors to recipients. *N Engl J Med* 1998;339: 1358-63.

132. Luppi M, Barozzi P, Santagostino G *et al.* Molecular evidence of organ-related transmission of Kaposi sarcoma-associated herpesvirus or human herpesvirus-8 in transplant patients. *Blood* 2000;96:3279-81.

133. Barozzi P, Luppi M, Facchetti F *et al.* Post-transplant Kaposi sarcoma originates from the seeding of donor-derived progenitors. *Nature Med* 2003;9:554-61.

134. Parravicini C, Olsen SJ, Capra M *et al.* Risk of Kaposi's sarcoma-associated herpesvirus transmission from donor allografts among Italian post transplant Kaposi's sarcoma patients. *Blood* 1997;90:2826-9.

135. Andreoni M, Goletti D, Pezzotti P *et al.* Prevalence, incidence and correlates of HHV-8/KSHV infection and Kaposi's sarcoma in renal and liver transplant recipients. *J Infect* 2001;43:195-9.

136. Marcelin AG, Roque-Afonso AM, Hurtova M *et al.* Fatal disseminated Kaposi's sarcoma following human herpesvirus 8 primary infections in liver-transplant recipients. *Liver Transpl* 2004;10:295-300.

137. Francès C, Marcelin AG, Legendre Ch *et al*; Skin and Organ Transplantation Group of the French Society of Dermatology. The impact of pre-existing or acquired Kaposi sarcoma herpesvirus infection in kidney transplant recipients on morbidity and survival. *Am J Transplant* 2009;9(11):2580-6.

138. Luppi M, Barozzi P, Schulz TF *et al.* Bone marrow failure associated with human herpes virus 8 infection after transplantation. *N Engl J Med* 2000;343: 1378-85.
139. Pietrosi G, Vizzini G, Pipitone L *et al.* Primary and reactivated HHV8 infection and disease after liver transplantation: a prospective study. *Am J Transplant* 2011;11:2715-23.
140. Lebbe C, Porcher R, Marcelin AG *et al*; Skin and Organ Transplantation Group of the French Society of Dermatology. Human herpesvirus 8 (HHV8) transmission and related morbidity in organ recipients. *Am J Transplant* 2013;13:207-13.
141. Riva G, Barozzi P, Quadrelli C *et al.* Human herpes virus 8 (HHV8) infection and related diseases in Italian transplant cohorts. *Am J Transplant* 2013;13: 1619-20.
142. Fu W, Merola J, Malinis M *et al.* Successful treatment of primary donor-derived human herpesvirus-8 infection and hepatic Kaposi sarcoma in an adult liver transplant recipient. *Transplant Inf Dis* 2018;20:e12966.
143. Dollard SC, Douglas D, Basavaraju SV *et al.* Donor derived Kaposi's sarcoma in a liver kidney recipient. *Am J Transplant* 2018;18:501-13.
144. Elliott WC, Houghton DC, Bryant RE *et al.* Herpes simplex type 1 hepatitis in renal transplantation. *Arch Intern Med.* 1980;140(12):1656-60.
145. Goodman JL. Possible transmission of herpes simplex virus by organ transplantation. *Transplantation* 1989; 47(4):609-13.
146. Al Midani A, Pinney J, Field N *et al.* Fulminant hepatitis following primary herpes simplex virus infection. *Saudi J Kidney Dis Transpl* 2011;22(1):107-11.
147. Shaw BI, Nanavati AJ, Taylor V *et al.* Donor derived HSV hepatitis in a kidney transplant recipient leading to liver fibrosis and portal hypertension. *Transpl Infect Dis* 2019;21(1):e13029. https://doi.org/10.1111/tid.13029.
148. Kaul D, Sharma T. Human T-cell lymphotrophic virus in solid-organ transplant recipients: Guidelines from the American Society of Transplantation Infectious diseases community of practice. *Clin Transplant* 2019; 33:e13575. https://doi.org/10.1111/ctr.13575.
149. Anuras S, Summers R. Fulminant herpes simplex hepatitis in an adult: report of a case in renal transplant recipient. *Gastroenterology* 1976;70:425-8.
150. Taylor RJ, Saul SH, Dowling JN *et al.* Primary disseminated herpes simplex infection with fulminant hepatitis following renal transplantation. *Arch Intern Med* 1981;141:1519-21.
151. Dummer JS, Armstrong J, Somers J *et al.* Transmission of infection with herpes simplex virus by renal transplantation. *J Infect Dis* 1987;155:202-6.
152. Koneru B, Tzakis AG, DePuydt LE *et al.* Transmission of fatal herpes simplex infection through renal transplantation. *Transplantation* 1988;45:653-6.
153. Foster MA, Weil LM, Jin S *et al.* Transmission of hepatitis A virus through combined liver–small intestine–pancreas transplantation. *Emerg Infect Dis* 2017; 23:590-6.
154. ECDC (European Centre for Disease Prevention and Control). Hepatitis A outbreaks in the EU/EEA mostly affecting men who have sex with men – second update, 19 May 2017. Stockholm: ECDC 2017, available at https://ecdc.europa.eu/sites/portal/files/documents/RRA-19-May-2017_UPDATE_2-HepatitisA-in-mostly-MSM.pdf, accessed 20 August 2020.
155. Werber D, Michaelis K, Hausner M *et al.* Ongoing outbreaks of hepatitis A among men who have sex with men (MSM), Berlin, November 2016 to January 2017 – linked to other German cities and European countries. *Eurosurveillance* 2017 Feb 02;22(5):30457. https://doi.org/10.2807/1560-7917.ES.2017.22.5.30457.
156. ECDC (European Centre for Disease Prevention and Control). Rapid risk assessment: hepatitis A outbreak in the EU/EAA mostly affecting men who have sex with men – third update. Stockholm: ECDC 2017, available at https://ecdc.europa.eu/sites/portal/files/documents/RRA%20hep%20A%20outbreak%20EU%20EEA%20in%20MSM%20third%20update%2028%20June%202017_0.pdf, accessed 20 August 2020.
157. Brock GN, Mostajabi F, Ferguson N *et al.* Prophylaxis against *de novo* hepatitis B for liver transplantation utilizing hep. B core (+) donors: does hepatitis B immunoglobulin provide a survival advantage? *Transpl Int* 2011;24:570-81.
158. Ouseph R, Eng M, Ravindra K *et al.* Review of the use of hepatitis B core antibody-positive kidney donors. *Transplant Rev* 2010;24:167-71.
159. Fishman, J. Infection in solid-organ transplant recipients, *N Engl J Med* 2007;357:2601-14.
160. Cirocco R, Zucker K, Contreras N *et al.* The presence of hepatitis B core antibody does not preclude kidney donation. Lack of viral DNA in the serum and biopsies of core antibody-positive donors and clinical follow-up. *Transplantation* 1997;63:1702-3.
161. Madayag RM, Johnson LB, Bartlett ST *et al.* Use of renal allografts from donors positive for hepatitis B core antibody confers minimal risk for subsequent development of clinical hepatitis B virus disease. *Transplantation* 1997;64:1781-6.
162. Huprikar S, Danziger-Isakov L, Ahn J *et al.* Solid organ transplantation from hepatitis B virus positive donors: consensus guidelines for recipient management. *Am J Transplant* 2015;15:1162-72.
163. Levitsky J, Doucette K, AST Infectious Diseases Community of Practice. Viral hepatitis in solid organ transplantation. *Am J Transplant* 2013;13:147-68.

164. Veyer D, Bardou-Jacquet E, Legros L *et al.* Natural history and virological lessons from *de novo* HBV infection in a vaccinated recipient of a liver graft from an anti-HBc positive donor. *J Liver Dis Transplant* 2013;2:1. https://doi.org/10.4172/2325-9612.1000106.
165. Hollinger F, Sood G. Occult hepatitis B virus infection: a covert operation. *J Viral Hepatitis* 2010;17:1-15.
166. Roggendorf M, Roß S. Definition und Diagnostik der akuten und chronischen Hepatitis B. *Z. Gastroenterology* 2004;42:679-81.
167. De Feo TM, Grossi P, Poli F *et al.* Kidney transplantation from anti-HBc+ donors: results from a retrospective Italian study. *Transplantation* 2006;81: 76-80.
168. Dhillon GS, Levitt J, Mallidi H *et al.* Impact of hepatitis B core antibody positive donors in lung and heart-lung transplantation: an analysis of the United Network for Organ Sharing. *Transplantation* 2009;88: 842-6.
169. Roche B, Roque-Afonso AM, Sebagh M *et al.* Escape hepatitis B virus mutations in recipients of antibody to hepatitis B core antigen-positive liver grafts receiving hepatitis B immunoglobulins. *Liver Transplant* 2010; 16:885-94.
170. Loggi E, Micco L, Ercolani G *et al.* Liver transplantation from hepatitis B surface antigen positive donors: a safe way to expand the donor pool. *J Hepatol* 2012; 56:579-85.
171. Cruzado JM, Gil-Vernet S, Castellote J *et al.* Successful treatment of chronic HCV infection should not preclude kidney donation to an HCV negative recipient. *Am J Transplant* 2013;13:2773-4.
172. Ellingson K, Seem D, Nowicki M *et al.* for the Organ Procurement Organization Nucleic Acid Testing Yield Project Team. Risk of human immunodeficiency virus and hepatitis C virus infection among potential organ donors from 17 organ procurement organizations in the United States. *Am J Transplant* 2011;11:1201-8.
173. Grebely J, Prins M, Hellard M *et al.* Hepatitis C virus clearance, reinfection, and persistence, with insights from studies of injecting drug users: towards a vaccine. *Lancet Infect Dis* 2012;12:408-14.
174. European Association for the Study of the Liver. EASL recommendations on treatment of hepatitis C 2018. *J Hepatol* 2018;69:461-511.
175. American Association for the Study of Liver Diseases and the Infectious Diseases Society of America. HCV guidance: recommendations for testing, managing, and treating hepatitis C. American Association for the Study of Liver Diseases and the Infectious Diseases Society of America, 2019, available at www.hcvguidelines.org, accessed 20 August 2020.
176. Hepatitis C transmission from seropositive, nonviremic donors to non-hepatitis C liver transplant recipients. *Hepatology* 2018;67:1673-82.
177. Natov SN, Lau JY, Ruthazer R *et al.* The New England Organ Bank Hepatitis C Study Group. Hepatitis C virus genotype does not affect patient survival among renal transplant candidates. *Kidney Int* 1999;56:700-6.
178. Morales JM, Campistol JM, Domínguez-Gil B *et al.* Long-term experience with kidney transplantation from hepatitis C positive donors into hepatitis C positive recipients. *Am J Transplant* 2010;10:2453-62.
179. Vargas HE, Laskus T, Wang LF *et al.* Outcome of liver transplantation in hepatitis C virus-infected patients who received hepatitis C virus-infected grafts. *Gastroenterology* 1999;117:149-53.
180. Gallegos-Orozco JF, Vargas HE, Rahela J. Virologically compromised donor grafts in liver transplantation. *J Hepatol* 2004;41:512-21.
181. Hézode C. Pan-genotypic treatment regimens for hepatitis C virus: advantages and disadvantages in high- and low-income regions. *J Viral Hepat* 2017; 24(2):92-101.
182. European Association for the Study of the Liver: EASL Recommendations on treatment of hepatitis C, 2016. *J Hepatol* 2017;66:153-94.
183. Jazwinski A, Muir A. The horizon: new targets and new agents. *Clinical Liver Disease* 2012;1:24-7.
184. Khan B, Singer LG, Lilly LB *et al.* Successful lung transplantation from hepatitis C positive donor to seronegative recipient. *Am J Transplant* 2017 Apr;17(4): 1129-31.
185. Sam T, Wada S, Joseph SM *et al.* Doing your best to keep the germs away. International Society for Heart and Lung Transplantation 2017, Annual Meeting 2017, Session 19, Abstract 0186 @ ISHLT 2017.
186. Bowring MG, Shaffer AA, Massie AB *et al.* Center-level trends in utilization of HCV-exposed donors for HCV-uninfected kidney and liver transplant recipients in the United States. *Am J Transplant* 2019;19(8): 2329-41. https://doi.org/10.1111/ajt.15355.
187. Friebus-Kardash J, Gäckler A, Kribben A *et al.* Successful early sofosbuvir-based antiviral treatment after transplantation of kidneys from HCV-viremic donors into HCV-negative recipients. *Transpl Infec Dis* 2019;21:e13146.
188. La Hoz R, Sandikci B, Ariyamuthu V, Tanriover B. Short-term outcomes of deceased donor renal transplants of HCV uninfected recipients from HCV seropositive nonviremic and viremic donors in the era of direct-acting antivirals. *Am J Transplant* 2019; 19:3058-70.
189. Molnar MZ, Nair S, Cseprekal O *et al.* Transplantation of kidneys from hepatitis C-infected donors to hepatitis C-negative recipients: single center experience. *Am J Transplant* 2019;19:3046-57.

190. Kilic A, Hickey G, Mathier M *et al.* Outcomes of adult heart transplantation using hepatitis C-positive donors. *J Am Heart Assoc* 2020;9:e014495.
191. Madan S, Patel SR, Rahgozar K *et al.* Utilization rates and clinical outcomes of hepatitis C positive donor hearts in the contemporary era. *J Heart Lung Transplant* 2019;38(9):907-17. https://doi.org/10.1016/j.healun.2019.06.023.
192. Kahn J, Terrault N. Intentional transmission of hepatitis C with organ transplantation: with opportunity comes responsibility. *Transplantation* 2019;103:2215-16.
193. Wadei HM, Pungpapong S, Cortese C *et al.* Transplantation of HCV-infected organs into uninfected recipients: advance with caution. *Am J Transplant* 2019;19:960-1.
194. Franchello A, Ghisetti V, Marzano A *et al.* Transplantation of hepatitis B surface antigen-positive livers into hepatitis B virus-positive recipients and the role of hepatitis delta coinfection. *Liver Transpl* 2005 Aug; 11(8):922-8.
195. Perrillo RP, Eason JD. The use of HBsAg-positive organ donors: far more than meets the eye. *Liver Transpl* 2005 Aug;11(8):875-7.
196. Lempp FA, Ni Y, Urban S. Hepatitis delta virus: insights into a peculiar pathogen and novel treatment options. *Nat Rev Gastroenterol Hepatol* 2016;13(10): 580-9. https://doi.org/10.1038/nrgastro.2016.126.
197. Lempp FA, Urban S. Hepatitis Delta virus: replication strategy and upcoming therapeutic options for a neglected human pathogen. *Viruses* 2017;9(7):172. https://doi.org/10.3390/v9070172.
198. Bogomolov P, Alexandrov A, Voronkova N *et al.* Treatment of chronic hepatitis D with the entry inhibitor myrcludex B: First results of a phase Ib/IIa study. *J Hepatol* 2016;65(3):490-8. https://doi.org/10.1016/j.jhep.2016.04.016.
199. Loglio A, Ferenci P, Uceda Renteria SC *et al.* Excellent safety and effectiveness of high-dose myrcludex-B monotherapy administered for 48 weeks in HDV-related compensated cirrhosis: a case report of 3 patients. *J Hepatol* 2019;71(4):834-9. https://doi.org/10.1016/j.jhep.2019.07.003.
200. Kamar N, Dalton HR, Abravanel F *et al.* Hepatitis E virus infection. *Clin Microbiol Rev* 2014;27:116-38.
201. Lee D, Zuckermann R. Herpes simplex virus infection in solid organ transplantation: guidelines from the American Society of Transplantation Infectious diseases community of practice. *Clin Transplant* 2019; 33:e13526.
202. Williams TP, Kasorndorkbua C, Halbur PG *et al.* Evidence of extrahepatic sites of replication of the hepatitis E virus in a swine model. *J Clin Microbiol* 2001;39:3040-6.
203. Legrand-Abravanel F, Kamar N, Sandres-Saune K *et al.* Hepatitis E virus infection without reactivation in solid-organ transplant recipients, France. *Emerg Infect Dis* 2011;17:30-37.
204. Schlosser B, Stein A, Neuhaus R *et al.* Liver transplant from a donor with occult HEV infection induced chronic hepatitis and cirrhosis in the recipient. *J Hepatol* 2012;56:500-02.
205. Pourbaix A, Quali N, Soussan P *et al.* Evidence of hepatitis E virus transmission by renal graft. *Transpl Infect Dis* 2017:e12624. https://doi.org/10.1111/tid.12624.
206. Tan HH, Leong HN, Tan BH *et al.* Chronic hepatitis e infection resulting in graft failure in a liver transplant tourist. *Case Rep Transplant* 2011;2011:654792.
207. Kamar N, Izopet J, Tripon S *et al.* Ribavirin for chronic hepatitis E virus infection in transplant recipients. *N Engl J Med* 2014 Mar 20;370(12):1111-20.
208. Thomas DL. A case for ribavirin to treat chronic hepatitis E. *N Engl J Med* 2014 Mar 20;370(12):1162-3.
209. Behrendt P, Steinamnn E, Manns M, Wedemeyer H. The impact of hepatitis E in the liver transplant setting. *J Hepatol*, 2014;61:1418-29.
210. Muller E, Kahn D, Mendelson M. Renal transplantation between HIV-positive donors and recipients. *N Engl J Med* 2010;362:2336-7.
211. Calmy A, van Delden C, Giostra E *et al.* Swiss HIV and Swiss Transplant Cohort Studies. HIV-positive-to-HIV-positive liver transplantation. *Am J Transplant* 2016 Aug;16(8):2473-8.
212. Hathorn E, Smit E, Elsharkawy AM *et al.* HIV-positive-to-HIV-positive liver transplantation. *N Engl J Med* 2016 Nov 3;375(18):1807-9.
213. Malani P. HIV and transplantation: new reasons for HOPE. *JAMA* 2016 Jul 12;316(2):136-8.
214. Ambaraghassi G, Cardinal H, Corsilli D *et al.* First Canadian case report of kidney transplantation from an HIV-positive donor to an HIV-positive recipient. *Can J Kidney Health Dis* 2017 Mar 2;4:2054358117695792.
215. Grossi P, Dalla Gasperina D, Morabito V *et al.* HIV-positive donors to HIV-positive transplant recipients: the Italian experience. Abstract No. 4396264 ESOT, *Transplant Int* 2019;32(supplement S2):160 [Special Issue: Abstracts of the 19th Congress of the European Society for Organ Transplantation, 15-18 September 2019, Copenhagen, Denmark], available at https://onlinelibrary.wiley.com/toc/14322277/2019/32/S2, accessed 23 June 2021.
216. Villa E, Petrini C, Venettoni S *et al.* Crisis management, ethical issues and the impact of HIV+ organ transplantation on donation in Italy. *Organs Tiss Cells* 2007;10:167-70.
217. Ison MG, Llata E, Conover CS *et al.* Transmission of human immunodeficiency virus and hepatitis C virus from an organ donor to four transplant recipients. *Am J Transplant* 2011;11:1218-25.

218. Library of Congress: Bill Summary & Status, 113th Congress (2013-14), S.330, Public Law 113-51 – Nov. 21, 2013 HIV Organ Policy Equity Act. Washington DC, 2013, available at www.gpo.gov/fdsys/pkg/PLAW-113publ51/pdf/PLAW-113publ51.pdf, accessed 20 August 2020.

219. *Federal Register: The Daily Journal of the United States Government*. Notice issued by the National Institute of Health (2015-11-25): Final Human Immunodeficiency Virus (HIV) Organ Policy Equity (HOPE) Act Safeguards and Research Criteria for Transplantation of Organs Infected with HIV. Department of Health and Human Services, National Institutes of Health. *Federal Register* 2015;80:34912-21, available at www.federalregister.gov/documents/2015/11/25/2015-30172/final-human-immunodeficiency-virus-hiv-organ-policy-equity-hope-act-safeguards-and-research-criteria.pdf, accessed 20 August 2020.

220. Muller E, Barday Z, Mendelson M *et al.* HIV-positive to HIV-positive kidney transplantation – results at 3 to 5 years. *N Engl J Med* 2015;327:613-20.

221. Stock PG, Barin B, Murphy B *et al.* Outcomes of kidney transplantation in HIV-infected recipients. *N Engl J Med* 2010;363:2004-14.

222. Terrault NA, Roland ME, Schiano T *et al.* for the HIV-TR Investigators. Outcomes of liver transplantation in HCV-HIV coinfected recipients. *Liver Transplant* 2012;18:716-26.

223. Grossi PA. Risk assessment for HIV+ organ donors: is the CD4 T cell count a marker of increased risk of transmissible diseases? *Transplantation* 2017 Apr; 101(4):684-5.

224. Etheredge HR, Fabian J, Duncan M *et al.* Needs must: living donor liver transplantation from an HIV-positive mother to her HIV-negative child in Johannesburg, South Africa. *J Med Ethics* 2019;45(5): 287-90. https://doi.org/10.1136/medethics-2018-105216.

225. ECDC (European Centre for Disease Prevention and Control). Geographical distribution of areas with a high prevalence of HTLV-1 infection. Stockholm: ECDC, 2015.

226. Toro C, Benito R, Aguilera A *et al.* Infection with human T lymphotropic virus type I in organ transplant donors and recipients in Spain. *J Med Virol* 2005; 76:268-70.

227. Ramanan P, Deziel PJ, Norby SM *et al.* Donor-transmitted HTLV-1-associated myelopathy in a kidney transplant recipient – case report and literature review. *Am J Transplant* 2014;14:2417-21.

228. Cook LB, Melamed A, Demontis MA *et al.* Rapid dissemination of human T-lymphotropic virus type 1 during primary infection in transplant recipients. *Retrovirology* 2016;13:3.

229. Yuzawa K, Matsuoka M, Yamano Y *et al.* High risk with human T-cell leukemia virus Type 1 for HTLV-1 associated myelopathy after living kidney transplantation in Japan. Abstract, 18th International Conference of Human Retrovirology, Tokyo, Japan, 2017.

230. Nakamura N, Tamaru S, Ohshima K *et al.* Prognosis of HTLV-I-positive renal transplant recipients. *Transplant Proc* 2003;37:1779-82.

231. Pillonel J, Le Marrec N, Girault A *et al.* [Epidemiological surveillance of blood donors and residual risk of blood-borne infections in France, 2001 to 2003] (in French). *Transfus Clin Biol* 2005 Jul;12(3):239-46. https://doi.org/10.1016/j.tracli.2005.04.032. PMID: 15963749.

232. ECDC (European Centre for Disease Prevention and Control). Risk assessment of HTLV-I/II transmission by tissue/cell transplantation. Part 1: Epidemiological review; and Part 2: Risks by tissue type, impact of processing and effectiveness of prevention measures. Stockholm: ECDC, 2012.

233. Mendoza C, Roc L, Benito R *et al.* HTLV-1 infection in solid organ transplant donors and recipients in Spain. *BMC Infect Dis* 2019;19(1):706. https://doi.org/10.1186/s12879-019-4346-z.

234. Hirsch HH, Randhawa P, AST Infectious Diseases Community of Practice. BK polyomavirus in solid organ transplantation. *Am J Transplant* 2013;13(Suppl 4):179-88.

235. Hirsch HH, Babel N, Comoli P *et al.* European perspective on human polyomavirus infection, replication and disease in solid organ transplantation. *Clin Microbiol Infect* 2014;20(Suppl 7):74-88.

236. Schmitt C, Raggub L, Linnenweber-Held S *et al.* Donor origin of BKV replication after kidney transplantation. *J Clin Virol* 2014;59:120-5.

237. Lorentzen EM, Henriksen S, Kaur A *et al.* Early fulminant BK polyomavirus-associated nephropathy in two kidney transplant patients with low neutralizing antibody titers receiving allografts from the same donor. *Virol J* 2020;17(1):5. https://doi.org/10.1186/s12985-019-1275-9.

238. Schwarz A, Linnenweber-Held S, Heim A *et al.* Viral origin, clinical course, and renal outcomes in patients with BK virus infection after living-donor renal transplantation. *Transplantation* 2016;100(4):844-53. https://doi.org/10.1097/TP.0000000000001066.

239. Wunderink HF, van der Meijden E, van der Blij-de Brouwer CS *et al.* Pretransplantation donor-recipient pair seroreactivity against BK polyomavirus predicts viremia and nephropathy after kidney transplantation. *Am J Transplant.* 2017;17(1):161-72. https://doi.org/10.1111/ajt.13880.

240. Hoffmann B, Tappe D, Höper D *et al.* A variegated squirrel Bornavirus associated with fatal human encephalitis. *N Engl J Med* 2015 Jul 9;373(2):154-62.

241. ECDC (European Centre for Disease Prevention and

Control). Rapid risk assessment: Acute encephalitis associated with infection with Borna disease virus 1, Germany. ECDC, 2019, available at https://ecdc.europa.eu/en/news-events/first-cases-borna-disease-virus-1-bodv-1-transmission-through-organ-transplantation, accessed 18 Aug 2020.

242. Niller HH, Angstwurm K, Rubbenstroth D *et al.* Zoonotic spillover infections with Borna disease virus 1 leading to fatal human encephalitis, 1999-2019: an epidemiological investigation. *Lancet Infect Dis* 2020;20(4):467-77. https://doi.org/10.1016/S1473-3099(19) 30546-8.

243. Schlottau K, Forth L, Angstwurm K *et al.* Fatal encephalitic Borna disease virus 1 in solid-organ transplant recipients. *N Engl J Med* 2018;379(14):1377-9. https://doi.org/10.1056/NEJMc1803115.

244. ECDC (European Centre for Disease Prevention and Control). Risk of transmission of Ebola virus via donated blood and other substances of human origin in the EU. Stockholm: ECDC, 6 October 2014 [available at www.ecdc.europa.eu/en/publications-data/risk-transmission-ebola-virus-donated-blood-and-other-substances-human-origin-eu, accessed 20 Aug 2020.

245. Kaul DR, Mehta AK, Wolfe CR *et al.* Ebola virus disease: implications for solid organ transplantation. *Am J Transplant* 2015;15:5-6.

246. ECDC (European Centre for Disease Prevention and Control). Middle East respiratory syndrome coronavirus (MERS-CoV). 21st update, 21 October 2015. Stockholm: ECDC, 2015.

247. Saudi Arabia Ministry of Health. Public Health events, available at www.moh.gov.sa/en/CCC/events/national/Pages/2020.aspx, accessed 5 Jun 2021.

248. AlGhamdi M, Mushtaq F, Awn N, Shalhoub S. MERS CoV infection in two renal transplant recipients: case report. *Am J Transplant*. 2015;15(4):1101-4. https://doi.org/10.1111/ajt.13085.

249. Gorbalenya AE, Baker SC, Baric RS *et al.* The species Severe acute respiratory syndrome-related coronavirus: classifying 2019-nCoV and naming it SARS-CoV-2. *Nat Microbiol* 2020;5(4):536-44. https://doi.org/10.1038/s41564-020-0695-z.

250. Bhimraj A, Morgan RL, Shumaker AH *et al.* Infectious Diseases Society of America Guidelines on the treatment and management of patients with COVID-19. *Clin Infect Dis* 2020;ciaa478. https://doi.org/10.1093/cid/ciaa478.

251. Arons MM, Hatfield KM, Reddy SC *et al.* Presymptomatic SARS-CoV-2 infections and transmission in a skilled nursing facility. *N Engl J Med* 2020;382:2081-90.

252. Kumar D, Humar A, Keshavjee, Cypel M. A call to routinely test lower respiratory samples for Sars-Cov-2 in lung donors. *Am J Transplant* 2021 Mar 23. https://doi.org/10.1111/ajt.16576.

253. Ritschl PV, Nevermann N, Wiering L *et al.* Solid organ transplantation programs facing lack of empiric evidence in the COVID-19 pandemic: a By-proxy Society Recommendation consensus approach. *Am J Transplant* 2020;20(7):1826-36. https://doi.org/10.1111/ajt.15933.

254. ECDC (European Centre for Disease Prevention and Control). Coronavirus disease 2019 (COVID-19) and supply of substances of human origin in the EU/EEA – 2nd update. ECDC, 2020, available at www.ecdc.europa.eu/en/publications-data/coronavirus-disease-2019-covid-19-and-supply-substances-human-origin, accessed 30 Sep 2021.

255. American Society of Transplantation. 2019-nCoV (Coronavirus): Recommendations and guidance for organ donor testing. AST 2020, available at www.myast.org/recommendations-and-guidance-organ-donor-testing, accessed 30 Sep 2021.

256. ISHLT (International Society of Heart and Lung Transplantation). Guidance from the ISHLT regarding the SARS CoV-2 pandemic. ISHLT 2021, available at https://ishlt.org/ishlt/media/documents/SARS-CoV-2_-Guidance-for-Cardiothoracic-Transplant-and-VAD-centers.pdf, accessed 30 Sep 2021.

257. The Transplantation Society. Guidance on Coronavirus Disease 2019 (COVID-19) for transplant clinicians. TTS TID 2020, available at https://tts.org/tid-about/tid-officers-and-council?id=749, accessed 30 Sep 2021.

258. Romagnoli R, Gruttadauria S, Tisone G *et al.* Liver transplantation from active COVID 19 donors: a lifesaving opportunity worth grasping? *Am J Transplant* 2021 Dec;21(12):3919-25. https://doi.org/10.1111/AJT.16823.

259. Schwartz BS, Mawhorter SD, the AST Infectious Disease Community of Practice. Parasitic infections in solid organ transplantation. *Am J Transplant* 2013; 13(Suppl 4):280-303.

260. Martín-Dávila P, Fortún J, López-Vélez R *et al.* The transmission of tropical and geographically restricted infections during solid organ transplantation. *Clin Microbiol Rev* 2008;21:60-96.

261. Hamilton KW, Abt PL, Rosenbach MA *et al.* Donor-derived *Strongyloides stercoralis* infections in renal transplant recipients. *Transplantation* 2011;91: 1019-24.

262. Kotton CN, Elias N, Delmonico FL *et al.* Case 15-2009: a 25-year-old man with coma after cardiac arrest. *N Eng J Med* 2009;360:2118-25.

263. Innes EA. A brief history and overview of *Toxoplasma gondii*. *Zoonoses Public Health* 2010;57:1-7.

264. OPTN (Organ Procurement and Transplantation Network). Ad Hoc Disease Transmission Advisory Committee. *Improving Post-Transplant Communication of New Donor Information, available at* https://optn.transplant.hrsa.gov/media/1873/dtac_policynotice_posttx_201606.pdf, accessed 18 Aug 2020.

265. Campbell AL, Goldberg CL, Magid MS *et al.* First case of toxoplasmosis following small bowel transplantation and systematic review of tissue-invasive toxoplasmosis following noncardiac solid organ transplantation. *Transplantation* 2006;81:408-17.

266. Vaessen N, Verweij JJ, Spijkerman IJ *et al.* Fatal disseminated toxoplasmosis after liver transplantation: improved and early diagnosis by PCR. *Neth J Med* 2007;65:222-3.

267. Assi MA, Rosenblatt JE, Marshall WF. Donor-transmitted toxoplasmosis in liver transplant recipients: a case report and literature review. *Transpl Infect Dis* 2007;9(2):132-6.

268. Montoya JG. Laboratory diagnosis of *Toxoplasma gondii* infection and toxoplasmosis. *J Infect Dis* 2002; 185(Suppl 1):S73-82.

269. Robert-Gangneux F, Sterkers Y, Yera H *et al.* Molecular diagnosis of toxoplasmosis in immunocompromised patients: a 3-year multicenter retrospective study. *J Clin Microbiol* 2015;53(5):1677-84.

270. Fernàndez-Sabé N, Cervera C, Fariñas MC *et al.* Risk factors, clinical features, and outcomes of toxoplasmosis in solid-organ transplant recipients: a matched case-control study. *Clin Infect Dis* 2012;54(3):355-61. https://doi.org/10.1093/cid/cir806.

271. Dhakal R, Gajurel K, Montoya JG. Toxoplasmosis in the non-orthotopic heart transplant recipient population, how common is it? Any indication for prophylaxis? *Curr Opin Organ Transplant* 2018;23(4): 407-16.

272. La Hoz RM, Morris MI; Infectious Diseases Community of Practice of the AST. Tissue and blood protozoa including toxoplasmosis, Chagas disease, leishmaniasis, Babesia, Acanthamoeba, Balamuthia, and Naegleria in solid organ transplant recipients – guidelines from the American Society of Transplantation Infectious Diseases Community of Practice. *Clin Transplant* 2019;33(9):e13546. https://doi.org/10.1111/ctr.13546.

273. WHO (World Health Organization). World Malaria Report 2019, available at www.who.int/publications/i/item/9789241565721, accessed 12 Jan 2022.

274. Mungai M, Tegtmeier G, Chamberland M, Parise M. Transfusion transmitted malaria in the United States from 1963 through 1999. *N Engl J Med* 2001;344(26): 1973-8.

275. Kitchen AD, Chiodini PL, Tossell J. Detection of malarial DNA in blood donors – evidence of persistent infection. *Vox Sang* 2014;107(2):123-31.

276. Schofield L, Mueller I. Clinical immunity to malaria. *Curr Mol Med* 2006;6:205-21.

277. Bousema T, Okell L, Felger I *et al.* Asymptomatic malaria infections: detectability, transmissibility and public health relevance. *Nat Rev Microbiol* 2014;12: 833-40.

278. Inoue J, Machado CM, Lima GFMdeC *et al.* The monitoring of hematopoietic stem cell transplant donors and recipients from endemic areas for malaria. *Rev Inst Med Trop Sao Paulo* 2010;52(5):281-4.

279. Pierrotti L, Echstein M, Di Santi S *et al.* Malaria disease recommendations for solid organ transplant recipients and donors. *Transplantation* 2018;102(25 Suppl. 2):S16-S26.

280. Rodriguez M, Tome S, Vizcaino L *et al.* Malaria infection through multi-organ donation: an update from Spain. *Liver Transpl* 2007;7:1302-4.

281. Lescure FX, Le Loup G, Freilij H. Chagas disease: changes in knowledge and management. *Lancet Infect Dis* 2010;10:556-70.

282. Chin-Hong PV, Schwartz BS, Bern C *et al.* Screening and treatment of Chagas disease in organ transplant recipients in the United States: recommendations from the Chagas in transplant working group. *Am J Transplant* 2011;11:672-80.

283. WHO (World Health Organization). WHO consultation on international biological reference preparations for Chagas diagnostic tests. Geneva: WHO, 2007, available at www.who.int/bloodproducts/ref_materials/WHO_Report_1st_Chagas_BRP_consultation_7-2007_final.pdf, accessed 12 Jan 2022.

284. Cura CI, Lattes R, Nagel C *et al.* Early molecular diagnosis of acute Chagas disease after transplantation with organs from *Trypanosoma cruzi*-infected donors. *Am J Transplant* 2013;13:3253-61.

285. Salvador F, Len O, Molina I *et al.* Safety of liver transplantation with Chagas disease-seropositive donors for seronegative recipients. *Liver Transplant* 2011;17: 1304-8.

286. Le M, Ravin K, Hasan A *et al.* Single donor-derived strongyloidiasis in three solid organ transplant recipients: case series and review of the literature. *Am J Transplant* 2014;14:1199-1206.

287. Arbeitskreis Blut at the Robert Koch Institut. Arbonematoden – durch Arthopoden übertragbare Nematoden-Infektionen. *Bundesgesundheitsbl.* 2012; 55:1044-56 (in German). https://doi.org/10.1007/s00103-012-1520-5.

288. Nordheim E, Storro MO, Natvik AK *et al.* Donor-derived strongyloidiasis after organ transplantation in Norway. *Transpl Infect Dis* 2019;21:e13008.

289. Malinis M, Boucher HW. Screening of donor and

candidate prior to solid organ transplantation – guidelines from the American Society of Transplantation Infectious Diseases Community Practice. *Clin Transplant* 2019;33:e13548. https://doi.org/10.1111/ctr.13548.

290. Román-Sánchez P, Pastor-Guzmán A, Moreno-Guillén S *et al.* High prevalence of *Strongyloides stercoralis* among farm workers on the Mediterranean coast of Spain: analysis of the predictive factors of infection in developed countries. *Am J Trop Med Hyg* 2003;69:336-40.
291. ECDC (European Centre for Disease Prevention and Control). Rapid risk assessment: local transmission of *Schistosoma haematobium* in Corsica, France – 16 May 2014. Stockholm: ECDC, 2014, available at www.ecdc.europa.eu/en/publications-data/rapid-risk-assessment-local-transmission-schistosoma-haematobium-corsica-france, accessed 20 August 2020.
292. Hoare M, Gelson WT, Davies SE *et al.* Hepatic and intestinal schistosomiasis after orthotopic liver transplant. *Liver Transplant* 2005;11:1603-7.
293. Cardiff and Vale University Health Board, Quality, Safety and Experience Committee: Renal transplant serious incident update, 2015, available at www.cardiffandvaleuhb.wales.nhs.uk/opendoc/258062, accessed 20 August 2020.
294. Capobianco I, Frank M, Königsrainer A *et al.* Liver fluke-infested graft used for living-donor liver transplantation: case report and review of the literature. *Transpl Infect Dis* 2015 Dec;17(6):880-5.
295. Gupte AA, Hocevar SN, Lea AS *et al.* Transmission of *Balamuthia mandrillaris* through solid organ transplantation: utility of organ recipient serology to guide clinical management. *Am J Transplant* 2014;14:1417-24.
296. Kaul DR, Covington S, Taranto S *et al.* Solid organ transplant donors with central nervous system infection. *Transplantation* 2014;98(6):666-70.
297. Trotter PE, Robb M, Hulme W *et al.* Transplantation of organs from deceased donors with meningitis and encephalitis: a UK registry analysis. *Transpl Inf Dis* 2016;18:862-71.
298. Copek M, McCullough J. Protein and biochemical changes during plasma exchange. In: Berkmann EM, Umlas J, eds. *Therapeutic hemapheresis*. American Association of Bloodbanks, Washington DC, 13-52, 1980.
299. Fehily D, Warwick R, Loty B. Tissue donation and banking. In: Manyalich M, Cabrer C, Paredes D *et al.*, eds, *Transplant co-ordination manual*. Barcelona: TPM Les Heures, Universitat de Barcelona, 2001: 251-68.
300. US DHHS: FDA (US Department of Health and Human Services: Food and Drug Administration). Guidance for industry. Screening and testing of donors of human tissue intended for transplantation. US DHHS: FDA, Washington DC 1997, available at www.hhs.gov/guidance/document/screening-and-testing-donors-human-tissue-intended-transplantation-guidance-industry, accessed 2 May 2022.
301. Department of Health. *SaBTO Microbiological safety guidelines*. Department of Health, London, 2020 revised edition, available at www.gov.uk/government/publications/guidance-on-the-microbiological-safety-of-human-organs-tissues-and-cells-used-in-transplantation, accessed 2 May 2022.
302. Eastlund T. Hemodilution due to blood loss and transfusion and reliability of cadaver tissue donor infectious disease testing. *Cell Tissue Bank* 2000;1:121-7.
303. Kitchen A, Gilian H. The serological screening of deceased tissue donors within the English Blood Service for infectious agents – a review of current outcomes and a more effective strategy for the future. *Vox Sang* 2010;98:e193-e200.
304. Barocas JA, Gauthier GM. Peritonitis caused by Blastomyces dermatitidis in a kidney transplant recipient: case report and literature review. *Transplant Infect Dis* 2014;16:634-41.
305. Krautkrämer E, Zeier M, Plyusnin A. Hantavirus infection: an emerging infectious disease causing acute renal failure. *Kidney International* 2012;83:23-7 (mini review).
306. Heymann P, Ceianu CS, Christova I *et al.* A five-year perspective on the situation of haemorrhagic fever with renal syndrome and status of the hantavirus reservoirs in Europe, 2005-2010. *Eurosurveillance* 2011;16(36): pii=19661, available at www.eurosurveillance.org/images/dynamic/EE/V16N36/art19961.pdf, accessed 2 May 2022.
307. Clemente WT, Mourão PHO, Lopez-Medrano F *et al.* Visceral and cutaneous leishmaniasis recommendations for solid organ transplant recipients and donors. *Transplantation* 2018;102(2S Suppl 2):S8-S15. https://doi.org/10.1097/TP.0000000000002018.
308. Jimenez-Marco T, Riera C, Girona-Llobera E *et al.* Strategies for reducing the risk of transfusion-transmitted leishmaniasis in an area endemic for Leishmania infantum: a patient- and donor-targeted approach. *Blood Transfus* 2018;16(2):130-6. https://doi.org/10.2450/2017.0201-16.
309. Colombo AL, Tobón A, Restrepo A *et al.* Epidemiology of endemic systemic fungal infections in Latin America. *Med Mycol* 2011;49(8):785-98. https://doi.org/10.3109/13693786.2011.577821.
310. Pannegeon V, Masini JP, Paye F *et al.* Schistosoma mansoni infection and liver graft. *Transplantation* 2005;80:287.
311. Lipowski D, Szablowska M, Perlejewski K *et al.* A

cluster of fatal tick-borne encephalitis virus infection in organ transplant setting. *J Infect Dis* 2017;15:896-901.

312. Huprikar S, Bosserman E, Patel G *et al.* Donor-derived *Trypanosoma cruzi* infection in solid organ recipients in the United States, 2001-2011. *Am J Transplant* 2013; 13:2418-25.

313. Wolfe C, Ison M. Donor-derived infections: guidelines from the American Society of Transplantation Infectious Diseases Community of Practice. *Clin Transplant* 2019;33:e13547.

314. Feldman A, Hsu E, Mack C. The importance of prioritizing pre and post transplant immunizations in an era of vaccine refusal and epidemic outbreaks. *Transplantation* 2020;104:33-8.

315. Danzinger-Isakov L, Kumar D, the AST Infectious Diseases Community of Practice. Vaccination in solid organ transplantation. *Am J Transplant* 2013; 13(Suppl 4):311-17.

316. Kotton C, Hibberd P, the AST Infectious Diseases Community of Practice. Travel medicine and transplant tourism in solid organ transplantation. *Am J Transplant* 2013;13(Suppl 4):337-47.

317. Höcker B, Böhm S, Fickenscher H *et al.* (Val)ganciclovir prophylaxis reduces Epstein–Barr-virus primary infection in pediatric renal transplantation. *Transpl Int* 2012;25:723-31.

Related material

Appendix 16. Hepatitis C – direct-acting antiviral drugs (HCV-DAA)
Appendix 17. Checklist for Covid-19 infection used in risk assessment of organ donors (United Kingdom)

Chapter 9. Risk of transmission of cancer

9.1. Introduction

Throughout this chapter, in order to simplify the wording, 'malignancy' describes malignant solid tumours as well as haematopoietic malignancies.

Malignancy can be transmitted to immunosuppressed recipients when organs from donors with known or unknown malignancies are transplanted [1-5]. With careful donor selection the chance of that happening is small, with approximately 0.05 % of organ recipients developing a donor-transmitted cancer [6-9]. The increasing use of older donors, in whom malignancy is more likely, might further increase the risk of transmission of occult cancer. The risk of transmission needs to be considered in the context of the important, life-enhancing and life-saving benefits afforded by organ transplantation. Nevertheless, due to the potentially serious consequences for the individuals affected and for donation and transplantation in general, potential donors must be carefully selected with the intention of minimising the risk of transmission of malignancy.

The increasing number of patients on waiting lists, along with the shortage of organs available for transplantation, has encouraged reconsideration of the criteria for acceptance of organs from donors with a past or current history of malignancy [8, 10, 11], acknowledging the key role of the medical teams in performing a risk–benefit assessment for each particular case (see Chapter 19) [12]. Proper characterisation of the donor and the organs is essential and is also a legal requirement for EU member states under Directive 2010/53/EU on standards of quality and safety of human organs intended for transplantation, and should include information on any previous cancer history and on the incidental finding of any malignancy in the donor.

This chapter provides professionals with recommendations for the screening of potential donors with regard to malignancies, and for the selection of organs from donors with a past or present history of malignancy. This chapter also provides professional guidance on identifying, reporting and assessing cases of potential and actual malignancy transmission. Meticulous assessment to confirm transmission of a donor cancer, rapid notification to appropriate agencies to alert those involved in the care of other potentially affected recipients, and careful management of the transplant recipient not only constitute responsible medical care but also provide the information upon which an evidence-based surveillance system can be built and applied.

Preventive measures recommended in all donor cases are discussed in section 9.2. Section 9.3 provides general recommendations for assessing the risk of malignancy transmission. Individual tumour types are analysed in sections 9.4 to 9.7. Donor transmission of oncogenic viruses is discussed in section 9.8, and donors with an underlying genetic predisposition to cancer are considered in section 9.9. For vigilance and surveillance regarding the detection and management of potentially transmitted tumours, see section 9.10.

9.2. General recommendations on detecting and assessing donor malignancy

9.2.1. Clinical history of the donor and physical examination

During donor evaluation, the complete clinical history of the donor should be reviewed. If possible, the donor's general practitioner and family members should be contacted to provide detailed information (see Chapter 6). The following basic points should be taken into consideration, though it may not always be possible to get exhaustive information about all of them during the process:

a. Lifestyle habits (e.g. smoking behaviour);

b. Recent suspicious features possibly related to malignancy, such as:

i. unintentional weight loss;
ii. special attention should be paid to potential hepatocellular carcinoma in HCV and/or HBV positive donors (even without cirrhosis), in donors with an alcoholic or non-alcoholic fatty liver disease or genetic haemochromatosis and in all donors with cirrhosis;
iii. a history of menstrual irregularities after pregnancies and/or miscarriages in women of child-bearing age may be clinical features of choriocarcinoma.

c. History of malignancy: records of any previously diagnosed malignancy (or tumours resected without documentation of the definite diagnosis) should be checked, with information obtained on:

i. date of first diagnosis;
ii. detailed histology (tumour type, stage, grade);
iii. previous imaging (staging, metastases);
iv. treatment received (surgery, chemotherapy and/or radiotherapy) including dates;
v. follow-up conducted, including imaging and last follow-up (dates, results, complete remission and/or tumour recurrence at any time);
vi. in cases of long-term survivors of cancers, special attention should be paid to possible second malignancies (e.g. metachronous colon cancer, years after primary colon cancer; new cancers after aggressive cancer therapies like radiotherapy-induced pleural mesothelioma and breast cancer; see §9.2.7).

d. Where donors present with a non-traumatic intracranial haemorrhage, an intracranial tumour or metastasis should always be excluded, especially if there was no history of arterial hypertension or arterio-venous malformations. In case of doubt, a pre- or intra-operative brain biopsy may be performed (see §9.2.5).

e. A family history should be taken to determine if there is a genetic predisposition to cancer in the donor (see §9.9).

A careful physical examination of the donor should be conducted, paying particular attention to the skin, looking for potential malignancy and scars of previous surgical procedures. Any suspicious finding requires clarification: e.g. any previous surgery should be checked for type and indication; any new suspicious naevus should be excised and sent for histopathological examination (before procurement if possible, but otherwise during procurement).

9.2.2. Laboratory determinations, tumour markers

Standard laboratory tests should be conducted in all potential donors with the objective of detecting specific diseases (including haematological malignancies) that may contraindicate organ donation.

Routine screening of tumour markers is not recommended, since false positive results may lead to unnecessary discard of suitable donors and organs. If requested as part of an individual centre's protocol, positive tumour markers should always be interpreted with other clinical findings and should never be the only factor leading to discarding an organ. If there is a confirmed malignancy in the donor history and previous tumour marker results are available, appropriate tumour markers should be tested to evaluate the current situation. These results should be compared with those from the time of first diagnosis and any results after subsequent treatment.

In women of child-bearing age with a history of menstrual irregularities, miscarriages or unexplained intracranial bleeding, levels of beta human chorionic gonadotropin (βHCG) may be determined to detect a choriocarcinoma.

9.2.3. Radiological tests and imaging studies

All radiological studies performed as part of the patient's hospital treatment should be reviewed along with the complete medical history and physical examination. Up-to-date studies at the time of donation should include, at minimum, chest radiographs (see Chapter 6). Further radiological investigations

(e.g. ultrasound and/or CT scans) may be required for thorough donor evaluation, especially in patients with suspected malignancy or in donors in whom it is thought that appropriate intra-operative examination of the thoraco-abdominal cavities cannot be adequately carried out. Existing imaging, including any trauma CT scans taken on admission, should be reviewed for evidence of malignancy, as well as to give a pre-operative indication of anatomical anomalies.

In patients with a history of cancer and where there is a possibility of tumour recurrence, whole-body CT scans of thorax, abdomen and pelvis should be carried out where possible to evaluate the current disease status and to ensure the highest possible safety for organ recipients [13]. Indeed, in many countries such as France and in Scandinavia, CT imaging is a routine part of donor work-up, and significant findings during screening are common [13-16]. Any suspicious finding on imaging should be further evaluated for its significance. Close communication with the radiologists is essential to assess the degree of suspicion for metastases or recurrent tumour. If there are explicit features of active malignancy, consideration should be given to stopping organ donation without further examinations. Where there is doubt about a radiological diagnosis of malignancy, histopathological examination should be performed during organ procurement. The organ donation process should not be abandoned hastily due to non-specific findings. Clarification of findings should always be sought in a reasonable timeframe wherever possible. Each case has to be evaluated and discussed very carefully, with a resulting joint decision. If the organ donation process is continued, the results have to be communicated to the accepting transplant centres.

9.2.4. Donor and organ examination during procurement

During organ procurement, surgeons should examine all intrathoracic and intra-abdominal organs (including the entire intestine and genitals), regardless of whether these organs are being considered for transplantation or not, in order to detect possible hidden tumours or pathological lymphadenopathy (see Chapter 11). Any suspicious lesion should be subject to immediate histological examination, preferably by a pathologist experienced in the organ in which the lesion was detected (see Figure 9.1 and Table 9.1) [13]. As recommended in section 6.2.5, this can be done through a regional network of pathologists who are within an acceptable range of transportation time.

Particular care should be taken when examining the kidneys, considering the relatively high number of benign and malignant tumours that have been found in kidneys following procurement. Removal of Gerota's fascia and of the peri-renal fat is essential, and this must be done at the time of procurement to ensure detailed inspection of the kidneys is completed before the kidneys leave the donor hospital. Recipient centres should be informed of any suspicious findings as a matter of urgency.

In spite of these measures small metastases or micrometastases may still be missed.

9.2.5. Histopathological examination

When a mass in any organ, or lymphadenopathy suspicious of malignancy, is found during the organ-procurement process, a histopathological examination must be performed using a cytological smear and/or histological section before any organ is transplanted (see Figure 9.1 and Table 9.1). The way the sample is taken and stored should be discussed with the examining pathologist; although frozen section biopsies are useful, more accurate opinions can often be gained from paraffin sections, which require the sample to be first placed in formalin. For example, accurate determination of the Fuhrman/nucleolar grade of a renal cancer is not usually possible on frozen section. However, paraffin section evaluation takes longer, and will not be appropriate where a decision on the safety of using the heart is needed, since it takes too long.

The mass should be resected completely to investigate potential malignancy properly, if possible without sacrificing an organ that is otherwise suitable for transplantation. The pathologist should be informed about all donor data and the macroscopic findings surrounding the suspicious mass, ideally with a photograph (see Chapter 6). It is preferable to send the whole tumour mass with a surrounding margin free of disease (e.g. Ro resection in space-occupying lesions in a kidney) to the pathologist.

Wherever possible, full histological characterisation of an intracranial space-occupying lesion should be performed before any organ is transplanted. Accurate neuroradiological diagnosis maybe possible for some types of brain tumour, but there remains the potential that the tumour may be of a different/higher grade than first thought. Post-donation autopsy may confirm the diagnosis and characterise the tumour exactly, but not in a timescale to inform use of organs with a shorter ischaemic time tolerance, such as the heart and lungs. Where no histological diagnosis exists, organs from a donor with an intracranial space-occupying lesion should only be used

in recipients whose probable waiting-list mortality justifies the extra risk, and only after fully informed consent has been given by the recipient or their next of kin. If there is a possibility that the space-occupying lesion is a metastasis then it is usually not safe to use any organ.

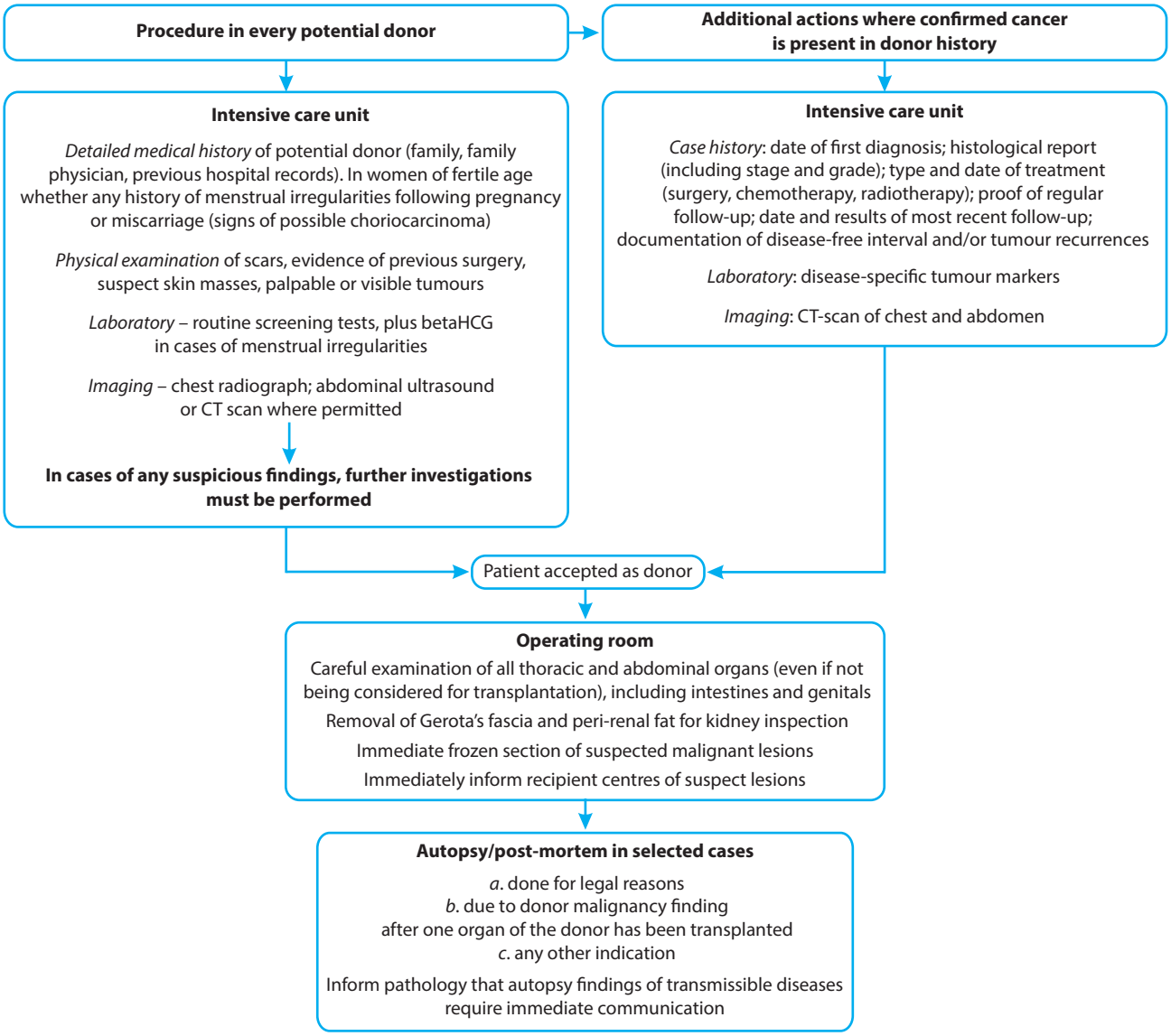
When a donor malignancy (primary tumour or metastasis) is identified shortly after organ procurement, such as during the implantation procedure, all recipient centres involved must be alerted immediately. In cases where organs have already been transplanted and subsequent histology reveals a malignancy (e.g. incidental cancer in a lung lobe discarded due to size reduction), a full donor autopsy should be requested whenever possible to obtain detailed information about tumour origin and dissemination.

Eccher *et al.* [13] describe their experience with 400 donors evaluated by the donor malignancy-screening protocol used in Verona, Italy. This detailed two-step protocol (ALERT 1: pre-operative evaluation; ALERT 2: intra-operative evaluation – both including histopathology if needed) led to identification of 73 malignancies, with 41 donors excluded early due to unacceptable transmission risk whereas the other 32 were confirmed by histopathology during ALERT

Table 9.1. **Confirmed diagnosis of donor malignancy**

When	How	What to do
Before donor assessment	Malignancy diagnosed from the patient's medical history	If donor organs are accepted despite a history of malignancy: • detailed histological reports, with staging and imaging studies as well as all information and actual diagnostic findings, must be documented on the donor information form; • transplant centres may take the decision to accept the organs; • oncologist advice can be sought; • informed consent should be obtained from the recipient/their family prior to transplantation; • careful follow-up should be undertaken, bearing in mind the possibility of transmission; • any possible transmission should be reported to the Health Authority in charge of serious adverse reactions or events (SAREs).
During donor assessment/ procurement and before transplantation	Malignancy found incidentally during clinical donor assessment or surgical inspection	If donor organs are transplanted despite malignancy being found during assessment: • urgent histological assessment (e.g. frozen section) should be performed immediately for preliminary diagnosis; subsequent work-up should be done for definitive diagnosis; • all recipient centres should be alerted immediately; • oncologist advice can be sought; • informed consent from the recipient should be sought prior to transplantation; • careful follow-up should be carried out, bearing in mind the possibility of transmission: • any possible transmission should be reported to the Health Authority in charge of SARE.
After transplantation of at least one organ	a. Frozen section misinterpreted as benign, final diagnosis malignant (e.g. initial interpretation oncocytoma, definitive interpretation RCC) or b. malignancy incidentally found during pre-transplant preparation of the organ in the recipient centre (other organs already transplanted) or c. donor autopsy results (available only after procurement and transplantation of organs) indicated malignancy or d. diagnosis in recipient within a few years of transplantation, e.g.: • histological finding of RCC; • suspicious mass on plain radiograph, ultrasound or CT scan; • symptomatic malignancy.	If donor organs are accepted and malignancy is found afterwards: • immediately alert organ procurement organisation and national Health Authority in charge of SARE; • Health Authority will alert all recipient centres and tissue establishments involved; • in situation b), especially in cases where metastases are detected, consider donor autopsy to identify origin and extent of the primary tumour (not necessary in case of solitary, completely resected small RCC pT1a); • joint decision of physician and recipient about further action (removal of transplanted organ, therapy) on the basis of a risk–benefit analysis; • carry out strict follow-up.

Figure 9.1. **Workflow: actions for detection/assessment of malignancy in potential organ donors**



1 or ALERT 2: the 32 were 12 prostate cancers, 7 renal cell carcinoma (RCC) and 13 others. Of these malignancies, 15 precluded donation due to unacceptable transmission risk, whereas 17 donors with acceptable malignancies proceeded to donation and transplantation. Three small donor cancers were missed by the protocol (8 mm hepatocellular carcinoma, and 3 mm and 5 mm breast cancers). They were diagnosed during donor autopsy after procurement, which was routinely performed in Verona until 2012.

Whenever only preliminary donor autopsy or biopsy results are available and final results are pending, all professionals involved should be advised on the importance of timely notification of the final results. Since autopsy findings are usually reported some time after the transplantation event, urgent requests for results may be helpful in these cases. Prompt communication is essential for the benefit of the recipients [17].

If no precise histological diagnosis of a suspicious mass can be obtained, the donor should be excluded unless the recipient is sufficiently sick and unlikely to get another offer, in which case the risk–benefit analysis may favour transplantation. It must be emphasised that the need to accept such risks would be exceptional, and should only be undertaken with the fully informed consent of the recipient or their family.

If a donor tumour is diagnosed after organs have already been transplanted, the recipients must be informed and should be involved in the decision whether removal of the graft and/or retransplantation may be appropriate. Initial results of frozen section must be interpreted with care (due to the technical limitations of the method) because final results might be different after paraffin embedding and special staining. See also Table 9.1.

9.2.6. Changes in the cancer staging system and classification of tumours

The classification of tumours is constantly being reviewed and updated, particularly following advances in molecular phenotyping, many of which are being incorporated into tumour classification. At the time of writing, the 8th edition (2016) is the most recent TNM staging system of the American Joint Committee on Cancer (AJCC) and the Union for International Cancer Control (UICC) [18]. The World Health Organization (WHO) also revised its classification of brain tumours in 2016 (see Table 9.4) [19], and this now incorporates both histologic and molecular features (e.g. glioblastoma, isocitrate dehydrogenase (IDH) mutant).

Therefore, in potential organ donors who are long-term survivors after cancer (e.g. > 5 years after tumour diagnosis and treatment) a different staging and classification system might have been in place at the time of first tumour diagnosis. Careful consideration should be given to the nomenclature used for staging and grading historically and currently.

Tumour staging and grading has evolved with time. Reassess the initial histopathological staging and grading of any cancer in light of the most recent knowledge.

9.2.7. Risk of second malignancy or complication in long-term survivors of previous malignancies

Frequently, in long-term survivors of aggressively treated malignancies, there is an increased risk of other *de novo* 'second' malignancies [20] (e.g. metachronous colon carcinoma; see §9.4.9) and malignancy in organs occurring as a consequence of treatment of the initial cancer with radiation or chemotherapy. This latter risk may include malignancies originating in an organ different to the one in which the primary tumour developed, e.g. pleural mesothelioma after thoracic radiotherapy for breast cancer, and breast cancer arising in females treated previously with mantle radiotherapy for lymphoma [21, 22].

In potential donors who are long-term survivors after a previous malignancy, diagnostic work-up should include consideration of the increased risk of developing a second malignancy.

9.3. General considerations to minimise the transmission of malignancy

9.3.1. Transmission risk and registry data

Although neither the exact frequency of donor malignancy nor the risk of malignancy transmission through organ transplantation is accurately known, there is some information based on the data available in the registries mentioned below. Additional data, from the many published case reports regarding all kinds of malignancy transmission, can serve as supporting information but cannot contribute to an accurate risk estimation.

When reviewing registry reports, caution is required as some historic reports cluster different tumour entities in one group (e.g. skin tumours, brain tumours) instead of describing definite diagnosis and staging information for individual donor tumour types, detail of which is mostly not available.

9.3.1.1. *The United Network for Organ Sharing Registry (United States)*

The first United Network for Organ Sharing (UNOS) report (1994-96) [23, 24] documented a 1.7 % incidence of donors with a history of cancer; 650 organs were transplanted from these 257 donors, with 85 % of organs from donors with cancers of skin (32 %), brain (29 %) or genito-urinary tract (24 %), but precise histological diagnosis and stage were not available in most cases. Of 188 transplants performed from donors with a history of central nervous system (CNS) cancer, primary diagnoses were available for only 42 cases, including 22 transplants from donors with a history of astrocytomas, 7 with glioblastomas, 6 with medulloblastomas, 4 with neuroblastomas and 3 from donors with a history of angioblastoma. It was noted that a number of cases without a histologic diagnosis probably included examples of benign meningiomas. In the case of donors reported to have skin cancer, only 4 of the 211 donors had melanomas while the remaining 207 had a history of non-melanoma skin cancer. The remaining donors had other specified types of cancer, including 38 with breast cancer, 11 thyroid and 9 lymphoma. Most had a recurrence-free interval of > 5 years before donation, and recipients had a post-transplant follow-up of 30 to 61 months. No transmission was reported.

A further UNOS report (1994-2001) [25] described 11 non-CNS malignancies transmitted into 15 (0.017 %) of 108 062 recipients of transplants during this period. The tumours transmitted were one melanoma (four recipients), one small-cell neuroendocrine tumour (two recipients), one adenocarci-

noma, one pancreatic cancer, one undifferentiated squamous cell carcinoma, two lung cancers, one renal tumour reported as oncocytoma, one papillary tumour of unknown origin, one breast cancer and one prostate cancer (from a donor with prostate adenocarcinoma with lymph node metastases found on organ procurement, with transmission to the heart recipient). They were diagnosed in the recipients between 3 and 40 months after transplantation (mean 14 months).

A more recent UNOS report (2000-05) [26] analysed 1 069 donors with a history of cancer and showed transmission of two donor tumours: one glioblastoma (with extracranial metastasis detected in the perioperative period) was transmitted to three recipients [27], and one malignant melanoma (resected 32 years before donation) was transmitted to one of six recipients. All affected recipients died of the transmitted tumours.

Two UNOS reports have looked specifically at donors with brain tumours. In the first (1992-99), UNOS reported no tumour transmission from 397 donors with CNS tumours (either confirmed in the history or listed as cause of death) from whom 1 220 recipients were transplanted (mean follow-up 36 months) [28]. Histology was recorded in only 7.5 %, but included 2 donors with medulloblastoma and 17 with glioblastoma, from whom 56 organs were transplanted with no transmission.

The most recent UNOS report (1987-2014) focuses on 337 recipients of thoracic organs from donors with brain tumours [29]. Histological tumour type was known in 89 cases, including 5 glioblastomas and one gliomatosis cerebri; there was no case of transmission.

9.3.1.2. *Organ Procurement and Transplantation Network Disease Transmission Advisory Committee (United States)*

Ison and Nalesnik [5] reported 28 confirmed donor-transmitted malignancies (seven RCCs, four lung carcinomas, two melanomas, one liver cancer, three pancreatic cancers, two ovarian cancers, two neuro-endocrine malignancies, six lymphomas and one glioblastoma) from 2005 to 2009. Nine recipients died of the transmitted tumours.

Green *et al.* [30] reported Disease Transmission Advisory Committee (DTAC) data for the year 2013 and showed five additional donor malignancies transmitted into eight recipients (three melanoma, two adenocarcinoma, three other malignancies) with two tumour-related deaths.

In 2011 Nalesnik *et al.* [8] suggested a new classification for assessing the clinical risk of donor malignancies (see §9.3.2).

9.3.1.3. *The Israel Penn International Transplant Tumor Registry*

The Israel Penn International Transplant Tumor Registry (IPITTR) [31] reported higher frequencies of malignancy transmission than other registries mentioned in this section. The discrepancy is explained by the fact that, due to the voluntary reporting of cases to IPITTR, only a small, selected cohort of patients are included in this registry and they are more likely to be reported if they suffered a transmission event. IPITTR does not cover the outcome of all recipients transplanted from donors with malignancy in the analysed time period. Donor malignancies would have escaped any documentation if none of the respective recipients suffered from transmission or if their follow-up data were incomplete.

Therefore the IPITTR data are generally considered to overestimate the malignancy transmission risk. According to the data up to 2001, of 68 recipients of organs from donors with RCC, tumour transmission was reported in 43. Of 30 recipients of grafts from donors with melanomas, tumour transmission occurred in 23 and, of the 14 recipients of grafts from organ donors with choriocarcinoma, there were 13 cases of tumour transmission. Over this same time period, other tumours were also transmitted, including lung, colon, breast, prostate and Kaposi sarcoma, as well as nine transmissions from 53 donors with CNS tumours. No transmission of thyroid, head and neck, hepato-biliary or testicular cancer or lymphoma/leukaemia was reported. Further extracted data, such as tumour transmission into cardiothoracic recipients [32, 33] or transplantation of kidneys with small renal cancers [34], have been published.

9.3.1.4. *United Kingdom Transplant Registry*

From a 10-year period (2001-10) with a total of 14 986 donors, Desai *et al.* [6] reported 15 transmissions (0.06 % of all recipients) of 13 occult donor malignancies (six renal cell cancers, four lung cancers, one lymphoma, one neuro-endocrine carcinoma, one colon carcinoma) with three subsequent recipient deaths.

In a second study, Desai *et al* [35] analysed 202 donors (1.1 % of all donors) from 1990 to 2008 with a history of cancer, including 61 donors with cancers classified as Unacceptable or High transmission risk according to international recommendations (25 glioblastomas, six medulloblastomas, 10 breast cancers, five lymphomas, four sarcomas, three melanomas, eight other malignancies). No transmission

was reported in 133 recipients of organs from these 61 donors.

Watson *et al.* [36] found no transmission from 177 donors with primary CNS malignancies in the years 1985-2001. Of these tumours, 33 were high-grade malignancies (24 WHO grade IV gliomas, nine medulloblastomas).

In 2014 the UK Advisory Committee for the Safety of Blood, Tissues and Organs (SaBTO) set out recommendations for the transplantation of organs from deceased donors with cancer or a history of cancer [11].

9.3.1.5. *The Organización Nacional de Trasplantes Registry (Spain)*

From 1990 to 2006, 117 donors with malignancy were reported (5.8 per thousand donors), all with tumours diagnosed after organ procurement [7]. Of these donors, five (0.29 per thousand donors) transmitted their malignancy into 10 recipients (0.06 % of all recipients in this period): one soft tissue sarcoma (three recipients), one germinal cell cancer (three recipients), one undifferentiated carcinoma (two recipients) and two RCC. These latter two cases were kidney recipients who were transplanted and later presented with a renal adenocarcinoma and a papillary carcinoma, respectively. In both cases the diagnosis was made through a biopsy after transplantation.

In 1996 the Organización Nacional de Trasplantes (ONT) issued recommendations about the use of organs from donors with malignancy. These recommendations inspired the first Council of Europe recommendations on risk levels for donor malignancy transmission.

9.3.1.6. *The Centro Nazionale Trapianti Registry (Italy)*

Since 2001, the Centro Nazionale Trapianti (CNT) has had a new strategy for evaluating the safety and acceptability of donors [37]. This strategy analyses donors with infections and tumours and has established some donor risk levels. Analysis of the years 2001-2002 showed a frequency of 2.9 % of potential donors with tumours. Approximately half of these were rejected as donors before procurement; in a quarter of cases the tumour was detected between organ procurement and transplantation; in the remainder, a malignancy was detected following transplantation. New data showed an improvement in diagnostic capabilities before and during organ procurement. Between 2006 and 2008, no cancers were transmitted following this risk-estimation approach [38].

Taioli *et al.* [39] analysed the outcome of 108 recipients who received organs from 59 donors with suspected or confirmed malignancy from 2002 to 2004, mostly non-CNS tumours. There was no evidence of tumour transmission after an average of 28 months.

Equivalent results were obtained in a subsequent analysis including 131 donors with malignancy from 2002 to 2005 (mostly prostate and RCC) by Zucchini *et al.* [15] and for 28 donors from 2003 to 2010 in southern Italy [40].

The latest update (2006-15) of 11 271 donors reports 415 with either a past or current history of cancer [41]. The most common cancers were: prostate in 112 cases, clear cell RCC in 46 cases and papillary RCC in 17. Five donors transmitted malignancy to 10 of the 29 858 recipients (0.03 %) in the study; none of the donors were known to have a cancer at the time of donation. Two donors transmitted lymphoma, and one each transmitted acute myeloid leukaemia, a primary intestinal tumour and an anaplastic tumour of unknown origin; nine of the 10 recipients died.

9.3.1.7. *MALORY – MALignancy in Organ donors and Recipient safetY (Germany)*

The MALORY study analysed data from a six-year period, 2006-11, of 248 organ donors with 254 malignancies (702 organs transplanted into 648 recipients) [9]. Follow-up information was collected in 2012 from 589 (91 %) recipients. There was no confirmed tumour transmission from donors whose malignancies were known before organ acceptance and transplantation (median recipient follow-up 576 days). The most frequent non-CNS malignancies were RCC (n = 35), breast cancer (n = 15), colorectal carcinoma (n = 11), prostate carcinoma (n = 12) and thyroid carcinoma (n = 9). They presented in different stages, with different grades and ranged from 'minimal risk' to 'unacceptable risk' according to international recommendations. The most frequent CNS malignancies were glioblastoma (n = 16) and anaplastic astrocytoma (n = 12). During the follow-up, 127 recipients (19.6 %) died of tumour-unrelated causes, and 135 recipients (23 %) were lost to follow-up (no follow-up data available after January 2011).

Nevertheless, tumour transmissions did occur in the cohort: seven donors without any suspected malignant disease transmitted their occult carcinoma (three RCCs, two neuro-endocrine tumours, one breast cancer, one colorectal cancer) into 13 recipients. As of October 2015, seven of these recipients had died as a result of the transmitted tumour (four liver, two kidney, one lung recipient). Three kidney recipients (neuro-endocrine and breast cancer) were disease-free after metastatic disease treated by

transplant nephrectomy, withdrawal of immunosuppression and chemotherapy. The three kidney recipients from donors with undetected RCC have never shown any clinical symptoms of the malignancy (all three kidney recipients had undergone transplant nephrectomy for either thrombosis or rejection post-transplant; pathological examination revealed incidental RCC).

The follow-up period is too short and the number of patients lost to follow-up is too high for final conclusions about transmission risk.

9.3.1.8. *Danish Registry Data*

Birkeland and Storm [42] linked all organ donors in a single transplant centre over a 27-year period to the Danish tumour registry. They identified 13 malignancies among 626 donors (2 %), of which eight were detected after the organs had been transplanted (1.3 %). Of those eight donors, only one transmitted the malignancy to the recipient, a melanoma (stage unknown at procurement) (0.2 %).

Cancer transmission through organ transplantation does occur. The number of organs accepted from donors with a previous or current history of malignancy seems to be increasing, but the frequency of documented cancer transmission is low. Underreporting of transmission cases due to previous lack of mandatory reporting cannot be ruled out. Within the EU legal framework [12], and with mandatory reporting to national Health Authorities of SARs (including suspected/confirmed cases of malignancy transmission), it should be possible in future to assess more precisely the frequency of malignancy transmission through organ transplantation.

9.3.2. Assessment of transmission risk

In cases where donor malignancy is diagnosed prior to or during organ procurement, a number of issues should be considered (see Table 9.2). In particular, it should be noted that:

a. Tumours that are newly diagnosed at procurement have to be evaluated very carefully. Organ donation is unlikely to proceed because very few types of active malignancy will be considered an acceptable risk. Testing for exact histological type and grade of the tumour is absolutely necessary as is accurate staging prior to acceptance and must be performed according to the latest international criteria: AJCC Cancer Staging Manual, 8th edition [18], and the 2016 WHO Classification of Tumors of the Central Nervous System [19].

b. In cases of treated malignancy in the patient's medical history, complete remission of 5 to 10 years (depending on tumour type, stage and grade) should have been achieved before the person is accepted for organ donation, although some exceptions exist. Careful assessment of the prognosis is recommended, taking into account the changes in tumour classifications that occurred in 2016, since the staging and grading of tumours diagnosed before then might differ slightly from current practice.

c. Patients with metastatic tumours (lymph node or distant metastases) should not be accepted as organ donors. Exceptions might be made in selected cases of tumours diagnosed > 5 years before procurement with an initial pN1 staging, full treatment and unsuspicious, recurrence-free follow-up with presumed cure.

d. Lack of surgical intervention, absent or incomplete follow-up or palliative therapy of malignancy in the patient's medical history are contraindications for organ donation (except for low-grade prostate cancer under active surveillance and certain brain tumours).

e. A donor with a previous malignancy must be evaluated carefully, both for evidence of recurrence of the malignancy and for the increased risk of a *de novo* malignancy. For example, a donor with a previous colon adenocarcinoma is at increased risk of developing a new colonic adenocarcinoma [43]. Therefore it is important to determine in the donor work-up the results and timing of any surveillance colonoscopies. Similarly, some cancer treatments predispose to new cancers, e.g. mantle radiotherapy for lymphoma and subsequent occurrence of breast cancer.

f. For a second opinion, advice from specialists in the relevant oncological field and/or from experienced pathologists may be sought to further assess the individual transmission risk.

g. Potential recipients of organs from donors with a history of cancer should be fully informed before consent for transplantation is obtained by the transplant centre. The extent of this informed consent should be based on a risk–benefit analysis and should enable the recipient to generate a realistic perception of the situation, but without provoking undue concern in cases of very low transmission risk.

Table 9.3 shows the current transmission-risk categorisations published by DTAC/USA [8], SaBTO/UK [11] and CNT/Italy [41]. The Council of Europe classification proposes a risk classification that con-

sciously omits any numerical estimation because of the limited evidence currently available. Details of the risk classification of specific tumours will be found in the subsections of 9.4 that follow.

The clinicians in charge of accepting and transplanting a graft have the overall responsibility for its use in a particular recipient, regardless of the estimated risks according to the classifications in Table 9.3.

9.3.3. Circulating tumour cells

Circulating tumour cells (CTCs) have been detected in the blood of many cancer patients – e.g. breast [45], colorectal [46], prostate [47] and glioblastoma [48, 49] – including early-stage cancers. Their existence has clinical impact on recurrence and survival in metastatic cancers. However, their relevance for the course of disease or the development of metastases in early stages is still under investigation. To be clinically relevant and cause metastases, CTCs need additional properties such as the ability to implant into favourable sites, protection from host-specific and non-specific immune responses (decreased in transplant patients) and the abilities to induce a blood supply and initiate growth. Accordingly, the fact that brain tumours rarely metastasise might in part be explained by the limited capacity of glioblastoma cells to exist outside the brain, even though 20-40 % of sufferers have CTCs [48, 49].

The probability of detecting CTCs in any kind of cancer correlates with the size of the sampling volume: in the case of large sample volumes (e.g. enrichment of cells by leukapheresis with 25 L of blood processed), CTCs might be detected with a high sensitivity. If only 10 mL of blood is tested in the setting of organ donation it is possible to obtain a false negative result due to the unrepresentative nature of the specimen [50, 51]. In addition to these technical difficulties and the limited experience in assessing the results, testing for CTCs is expensive and time-consuming, and the reliable detection of CTCs is dependent on the availability of an experienced laboratory. Therefore, searching for CTCs in organ donors is currently not appropriate, though it might become a valuable method in the future.

9.4. Solid organ tumours

Acceptance of donors with a history of malignancy varies among European countries as well as worldwide. Published recommendations [5, 11, 41, 52] classify the different tumour entities according to their estimated transmission risk. This is based on the available literature, national data, expert opinions and data on tumour behaviour in non-transplant patients. In general, it is supposed that donors with tumours that are presumed to have been cured – after full treatment, adequate strict follow-up and without suspicion of disease recurrence or metastases – can be accepted for selected recipients, with an awareness of a remaining transmission risk.

Probability of cure and the risk of metastases differ among the various tumours depending on their histological type, stage, grade and treatment, and these have to be taken into account. For example, an oesophageal cancer pT1N0M0 will be assessed differently after a recurrence-free survival of 2 years versus 25 years. Thus, the below-mentioned risk criteria may decrease for presumed cured donor cancers, but current literature does not provide sufficient data for definitive statements. There is no international consensus on a required time of recurrence-free follow-up, and national recommendations may vary from >5 or >10 years to never, for the same tumour type and stage.

An individual risk–benefit assessment must be performed for every potential recipient. The permissive environment for growth of transmitted tumours in an immunosuppressed recipient should also be taken into account.

Informed consent should be obtained from the recipient or their legal representative.

Every recipient who receives an organ from a donor with a history of malignancy should be offered additional testing, monitoring and treatment as appropriate, in addition to routine follow-up care (UNOS/OPTN policy 15.5.A) [53].

This Guide provides recommendations to assist in assessing different types of malignancy. To apply these recommendations in clinical practice, donor evaluation should be as complete as possible in accordance with Chapter 6 and also section 9.2, Table 9.1 and Table 9.2. In cases of doubt, the relevant national and individual strategy should be discussed with national experts.

The following alphabetical listing (§9.4.1 to §9.4.31) covers the most common cancers in terms of incidence and mortality in Europe [54], as well as other frequently reported donor malignancies. Considerations about transmission risk and acceptability are also included for malignancies that are not mentioned in any literature on organ donation but that are increasingly referred to in requests regarding the acceptance of potential organ donors.

Table 9.2. **Items to consider for a potential organ donor with a current or past history of cancer**

Donor-related	Active tumour	What is the specific type of tumour? What is the extent of tumour, i.e. tumour stage? What is the risk of tumour transmission based on current available evidence?
	Historical tumour	All of the above, and also: How long ago did the tumour occur? What is the tumour-free interval? Is this tumour associated with late recurrence? What is the expected 5-year disease-free survival? Did the donor receive curative treatment for the tumour? Has there been adequate follow-up following treatment?
Recipient-related	What is the desire of the potential recipient? Is there a clear understanding of the risks involved? What type of post-transplant screening would be appropriate in this circumstance? For how long? What treatment options are available if tumour is transferred? What are the alternatives for this patient if transplantation is deferred because of concerns about tumour transmission?	

Source: modified after Nalesnik and Ison [44]

Table 9.3. **International recommendations for the assessment of transmission risk of donor malignancies**

CNT/Italy 2015	DTAC/USA 2011	SaBTO/UK 2014	Council of Europe 2020
Standard risk	No significant risk	—	—
Non-standard – negligible risk	Minimal risk (< 0.1 %)	Minimal risk (< 0.1 %)	Minimal risk Donor acceptable for all organs and all recipients
Non-standard – acceptable risk	Low risk (0.1-1 %)	Low risk (0.1-2 %)	Low to intermediate risk Donor acceptable, justified by the specific health situation of the recipient or the severity of their clinical condition, based on a risk–benefit analysis
	Intermediate risk (1-10 %)	Intermediate risk (2-10 %)	
	High risk (> 10 %)	High risk (> 10 %)	High risk Acceptance may be discussed in exceptional cases and for some life-saving transplantation procedures in the absence of any other therapeutic options on a case-by-case basis, after careful and reasonable risk–benefit assessment and informed consent of the patient
Non-standard – unacceptable risk	—	Absolute contraindication	Unacceptable risk Absolute contraindication due to active malignancy and/or metastatic disease
—	Unknown risk (not equivalent to absolute contraindication)	—	—

9.4.1. Adrenal tumours

Adrenal (suprarenal) tumours are occasional findings on examination of the kidneys. Histologically, it is not possible to determine whether a primary adrenal tumour, either medullary or cortical, is malignant or benign; the adrenal gland is, however, a common site for metastases, so frozen section examination to rule out a secondary cancer is worthwhile.

Medullary phaeochromocytomas are discussed in detail in section 9.4.16.

There are no reports of transplantation of organs from donors with adrenocortical tumours.

9.4.2. Appendiceal tumours

Tumours of the appendix are commonly neuroendocrine tumours (see §9.4.16), but adenocarcinomas and cystadenomas also occur. Appendiceal carcinoids less than 2 cm (pT1) rarely metastasise, with none reported in a series of 127 subjects [55, 56].

Adenocarcinomas are frankly malignant but cystadenomas, which present with appendiceal mucoceles, are on a spectrum from benign to malignant.

There are no reports of donors with appendiceal carcinomas or neuro-endocrine tumours.

Appendiceal tumour diagnosed during donor procurement

The presence of an appendiceal tumour is a contraindication to donation.

Appendiceal non-neuroendocrine tumour in donor history

Organs from donors with non-neuroendocrine appendiceal tumours in the donor history may be used in selected cases if fully treated and a recurrence free period of >5 years with the probability of a cure.

Appendiceal neuroendocrine tumour in donor history

A well-differentiated carcinoid tumour < 2 cm (pT1) without lymph node or distant metastases is assumed to have a low transmission risk after adequate excision and disease-free survival of > 5 years. Risk increases with size/stage, and probability of presumed cure has to be taken into account.

9.4.3. Basal cell carcinoma

See section 9.4.15.

9.4.4. Biliary cancer

See section 9.4.17.

9.4.5. Bladder cancer (non-urothelial)

There are no reports of donors with current or historical, non-urothelial bladder cancer from which to draw evidence. For urothelial (transitional cell) cancer of the ureter, see section 9.4.30.

Approximately 5 % of bladder cancers are squamous cancers, although it is more common where schistosomiasis is prevalent. It is also associated with indwelling catheterisation and other chronic inflammatory processes. It has a poorer prognosis than urothelial bladder cancers. There are no reports of donors with squamous bladder cancers.

9.4.6. Breast cancer

Since breast cancer has high potential for late and aggressive recurrence and metastasis, even after many years of complete remission, patients with this cancer should only be accepted as organ donors for very selected recipients and with the highest caution.

Friedman *et al.* reported 9 patients receiving organs from 8 female donors with a history of breast cancer (two were diagnosed 0.3 and 16 months following living donation); there were two cases of breast cancer transmission in kidney recipients at 4 and 12 months after transplantation [57]. One male recipient died, and the other was disease-free for 36 months after withdrawal of immune-suppression and anti-oestrogen therapy. Buell *et al.* referred to a 29 % rate of transmission of invasive breast cancer in cases reported to the voluntary IPITTR, with no transmission in donors with a history of duct or lobular carcinoma *in situ* [58]; the actual number of cases is not reported, but may have included the cases reported by Friedman *et al.* [57]. A case of transmission of an occult ductal breast adenocarcinoma from a living kidney donor was also reported by Kauffman *et al.* [25]. The kidney recipient rejected graft and tumour after cessation of immunosuppression and was relisted for transplant after a recurrence-free survival of 4 years. The cancer was diagnosed 6 months post-transplant, making it unlikely that this is one of the cases reported previously.

Transmission of an occult metastatic donor breast cancer into four recipients was reported by Moench *et al.* [9] and Matser *et al.* [59], first diagnosed in the double-lung recipient 2 years after transplantation. The lung and the liver recipient as well as one kidney recipient died of the transmitted tumour. The other kidney recipient showed complete remission of the transmitted metastatic disease after transplant nephrectomy, withdrawal of immunosuppression and chemotherapy.

Donor breast cancer transmission confined to a keratolimbal allograft has been reported, manifesting 4 years after transplantation [60].

As in malignant melanoma, tumour cell dormancy is a well-recognised phenomenon with breast cancer. Tumour cells spread to distant sites early during cancer progression. They can stay dormant and clinically undetectable after resection of the primary tumour for many years. Metastasis in breast cancer usually manifests asynchronously with the primary tumour and shows variable time to become clinically detectable [61, 62]. Therefore, an extended cancer-free period before accepting a donor with breast cancer is recommended, reliably performed follow-up should be ascertained and current donor examination for metastases including imaging are necessary, even after a long disease-free survival.

The original histology report should be reviewed for details of receptor expression of oestrogen/progesterone (E/P) and HER2/neu. E+/P+ is associated with a favourable prognosis, but expression of HER2/neu+ results in a poorer outcome in the general oncological setting [63, 64].

Carcinoma *in situ* is a non-invasive tumour that has not crossed the basement membrane (see §9.4.7). Lobular carcinoma *in situ* is now considered a benign disease and has been removed from TNM staging in

the last AJCC revision [18], although its presence is associated with a risk of developing invasive breast cancer in the future. High nuclear grade *in situ* breast cancer is thought to be more aggressive than breast cancer *in situ* without high-risk features because it entails the possibility of undetected micro-invasive carcinoma as well as carrying a higher risk of developing invasive disease [65-67]. Duct carcinoma *in situ* (DCIS) is considered low to intermediate risk of transmission.

Breast cancer diagnosed during donor procurement

Newly diagnosed invasive breast cancer is an unacceptable risk for organ donation.

Breast cancer in the donor history

Organs from donors with invasive breast cancer might be accepted in selected cases after full treatment, complete remission and stringent follow-up for > 5 years, depending on the initial stage and E/P and HER2/neu receptor expression, always bearing in mind the risk of transmission due to possible late metastases.
Breast cancer stage 1A (T1, N0; AJCC, 8th edition) [18] with curative surgery and cancer-free period > 5 years seems to be associated with low to intermediate risk for transmission. All other invasive breast cancer stages are considered high-risk for transmission, independent of the presumed recurrence-free survival and treatment.
High nuclear grade DCIS is considered low to intermediate risk for transmission.

9.4.7. Carcinoma *in situ*, pancreatic and biliary intra-epithelial neoplasia

Carcinoma *in situ* is a non-invasive epithelial tumour that has not crossed the basal lamina. Therefore, it has no potential for metastases, but can transform into an invasive tumour after some time.

Historical recommendations contraindicated transplants from potential donors with very aggressive malignancies, such as melanoma or lung cancer, for any stage of the disease, even in cases of *in situ* tumours [68]. Since carcinoma *in situ* is a very early, non-invasive tumour stage [69], patients with these diagnoses might be acceptable as organ donors with increased caution.

Carcinoma in situ, PanIN and BilIN diagnosed during donor procurement or in donor history

Many *in situ* carcinomas – e.g. uterine cervix, colon, breast (only low-grade), non-melanoma skin and vocal cord, together with pancreatic intra-epithelial neoplasia (PanIN) or biliary intra-epithelial neoplasia (BilIN) in the absence of invasive cancer, may be considered minimal risk. Transplantation of a pancreas with PanIN or a liver with BilIN is not recommended.
Regarding the non-muscle-invasive urinary bladder cancers, *in situ* urothelial cancer (pTis) and intra-epithelial papillary urothelial carcinoma (pTa/G1-2) – see AJCC, 8th edition [18] – are considered minimal risk for non-renal transplants. Renal transplants from these donors should be considered as a higher risk for transmission due to the often multifocal character of transitional cell cancers and the higher risk of cancer in the renal pelvis.
High-grade *in situ* breast cancer, *in situ* lung cancer and *in situ* melanoma/lentigo maligna are considered low to intermediate risk for transmission.

9.4.8. Choriocarcinoma

Choriocarcinoma is a highly aggressive cancer originating from trophoblastic tissue after hydatidiform mole, miscarriage or ectopic/intra-uterine pregnancy. IPITTR reports a high (93 %) transmission rate and a high (64 %) recipient mortality rate [58], although these incidences are likely to be overestimates. Nevertheless occasional cases of unrecognised donor choriocarcinoma resulting in multiple transmissions continue to be reported [70]. In a review of donor cancer transmission in renal transplant recipients, five cases of choriocarcinoma were described that presented a median one month post-transplant [71].

In cases where choriocarcinoma is suspected (e.g. menstrual irregularities, cerebral haemorrhage in a woman without risk factors), assays for βHCG in the urine or blood (e.g. in cases of renal impairment of the donor) should be carried out, since βHCG levels are increased in females with choriocarcinoma. Due to the rare occurrence of this tumour, no extensive donor data for a modified risk classification are to be expected in the future.

Choriocarcinoma diagnosed during donor procurement

Due to the high transmission and mortality rates, it is considered an unacceptable risk for organ donation in any stage of disease.

Choriocarcinoma in the donor history

Due to the reported high transmission and mortality rates, it is considered to be associated with a high or unacceptable risk for transmission through organ donation, depending on the recurrence-free period prior to donor death.

9.4.9. Colorectal cancer

There are two case reports describing metastatic transmission of occult colorectal carcinoma of the

donor into liver recipients [72, 73]. In one case, liver metastases of donor origin were diagnosed 18 months after transplantation. Retransplantation was not considered because of the patient's reduced health condition. The recipient died a few months later. In the second report, colorectal metastases were detected in the allograft 13 months after transplant. Following transplant hepatectomy and retransplantation, the patient remained tumour-free, dying three years later from recurrent hepatitis C. Kidney, cornea and heart-valve recipients from the same donor did not develop tumours post-transplant. The two donors were 69 and 68 years old respectively.

Clearly, these rare but potentially devastating cases should remind procurement surgeons to carefully examine all intra-abdominal and intra-thoracic structures for suspicious lesions, particularly in older donors.

In donors with a past history of colorectal cancer, the higher chance of a new colorectal cancer – a metachronous tumour, incidence of around 3 % at 10 years [43, 74] – should be borne in mind when examining the abdominal contents during organ procurement.

Buell *et al.* [58] describe a 19 % transmission risk for organs from donors with a history of colon cancer but reported the risk to be under 1 % for T1 tumours; full details were not reported. Several registries have reported donors with a history of colon cancer without subsequent disease transmission [5, 9, 26, 35, 39-42] (see §9.3.1), while the IPITTR reported two transmissions from five living kidney donors with colon cancer (possibly the same cases as Buell *et al.*) [4]. A separate Brazilian report details two renal recipients developing a donor-transmitted cancer of intestinal origin, possibly large bowel [75].

Colorectal cancer diagnosed during donor procurement

Donors with pT1 tumours (where pT1 is defined in AJCC 8th edition [18]) should only be accepted for organ donation with the utmost caution, and a high transmission risk must be assumed. Patients with higher stages of newly diagnosed, active colorectal cancer should not be accepted for organ donation (unacceptable risk).

Colorectal cancer in donor history

The presence of pT1/pT2 (Dukes' A or B) colorectal carcinoma (infiltration of submucosa/ muscularis propria) in the donor without lymph node or distant metastases is assumed to have a low transmission risk after adequate treatment and disease-free survival of > 5 years. Risk increases with stage, and probability of presumed cure has to be taken into account.

In the past there has been discussion as to whether donors with early stages of colorectal cancer (pT1, infiltration of submucosa) might be acceptable, even in cases of a newly diagnosed, unresected tumour. However, submucosal infiltration depth (sm1-3), lymphovascular invasion (L0-1), tumour budding and microsatellite instability also have significant influence on the risk of lymph node and distant metastases in pT1 tumours [76-78]. This suggests caution should be exercised in considering organs from a donor with recently diagnosed pT1 colorectal cancer. In these cases, thorough diagnostics should be provided but will not be available in time when a tumour is detected during organ procurement.

9.4.10. Gastric cancer

See section 9.4.17.

9.4.11. Gastrointestinal stromal tumour

Gastrointestinal stromal tumours (GIST) are the most common mesenchymal tumours and account for 5 % of all sarcomas. They are mostly detected as very small lesions in the walls of the stomach and/or small intestine, but can also be found in colon or rectum.

The risk of progression and metastases is correlated to four main prognostic factors [79]: tumour localisation, mitotic count (tumour cell proliferation), tumour size and tumour rupture before or during surgery.

Gastric or duodenal GIST < 2 cm, with mitotic index < 5 per 50 high power fields, have a low risk of metastases. Complete excision is accepted as the only treatment. These GISTs do not necessarily contraindicate organ donation. Rectal or jejunal GIST, size ≥ 2 cm or mitotic index ≥ 5 per 50 high power fields, are associated with higher risk of metastases and thus transmission [80].

Fiaschetti *et al.* [40] reported a single donor with confirmed gastric GIST without evidence of transmission to the recipients. Subsequently Novelli *et al.* [81] summarised five cases of GIST diagnosed in a single centre during donor procurement (three stomach, one ileum, one colon). After the suspicion of GIST on the frozen section, all five were confirmed to be low-grade (due to very few or no mitoses) GIST on permanent section and immunohistochemistry. Three organs (two kidneys from donor 1 and the liver from donor 2) were transplanted with no sign of tumour transmission after 18 and 46 months.

Frozen section histology may help to identify GISTs with a very low potential risk of transmission.

Mitotic count evaluation as well as the search for presence of c-kit (CD117) or DOG1 are performed on permanent sections but are typically not available as a frozen section assessment.

GIST diagnosed during donor procurement

Small (< 2 cm) GIST of the stomach or duodenum may be acceptable for organ donation with a low-to-intermediate risk for transmission. Mitotic index should be determined, though results are only likely to be available after transplantation of the organs. GIST from other primary sites, of larger size or high mitotic count, are associated with an increased risk of metastases and a high risk of transmission.

GIST in the donor history

Small (< 2 cm) GIST of the stomach or duodenum and mitotic count < 5 % may be acceptable for organ donation with a low-to-intermediate or even minimal risk of transmission, depending on therapy, follow-up time and recurrence-free survival. GIST from other primary sites, of larger size or high mitotic count, are associated with an increased risk of metastases and a high risk of transmission. No detailed information or recommendations are available from the literature.

9.4.12. Liver cancer

See section 9.4.17.

9.4.13. Lung cancer

Several registries [5, 6, 25, 58] and case reports [82-86] have described transmission of an occult donor lung cancer (including some small-cell carcinomas), mostly resulting in the death of the recipient. This suggests that transmitted lung cancers behave very aggressively in organ recipients. The transplant clinician should be especially aware of this possibility in the case of a donor with a heavy smoking history.

Jaillard *et al.* [87] report a case of small-cell lung cancer detected in the donor 7 months after living kidney donation. Transmission was confirmed in the asymptomatic recipient, who underwent transplant nephrectomy and three cycles of chemotherapy. Complete metabolic response could be demonstrated by FDG PET/CT 12 months thereafter but long-term outcome has not yet been reported.

A recent systematic review [71] of tumour transmission after renal transplantation showed nine cases of lung cancer with a median onset time of 13 months post-transplant and with metastatic disease at presentation in seven of nine patients. Among patients with donor-transmitted cancers, those with either lung cancer or melanoma had the worst prognosis. (See also §9.4.14.)

Two separate reports of lung cancer transmission to liver recipients attest to a poor outcome in this recipient group. In one case an autopsy performed the day after donation on a 63-year-old ex-smoker with a 10 pack year history revealed a lung mass with metastatic nodal involvement. Liver retransplantation was undertaken on day 7, with no tumour identified in the explanted donor liver. Eleven months later the recipient developed metastatic adenocarcinoma of the lung confirmed to be from the first donor; he died four weeks later [88]. In a separate case, four months after transplantation, a liver recipient developed metastatic deposits of a poorly differentiated tumour with mixed features of small-cell and non-small-cell carcinoma, identified to be of donor origin. Retransplantation was not undertaken and he died shortly afterwards with evidence of extra-hepatic disease [86].

For recommendations regarding *in situ* lung cancer go to section 9.4.7.

Lung cancer diagnosed during donor procurement

Any histotype of newly diagnosed lung cancer is an unacceptable risk for organ donation.

Lung cancer in the donor history

Treated lung cancer is considered to be associated with a high transmission risk. Risk may decrease after curative therapy, with recurrence-free time and with increasing probability of cure.

9.4.14. Malignant melanoma

Malignant melanoma transmission rates of 74 % have been reported from the IPITTR with a 60 % recipient mortality rate [58]. This is likely to be an overestimate, but transmission events continue to be described in case reports and in recent registry data [5, 26, 30, 42, 89, 90]. Most cases of reported donor-transmitted melanoma were cases where tumour diagnosis was missed in the donor [58, 91, 92]. In a review of case reports in 2010, Strauss et al [93] described 13 donors of 30 transplanted organs, with 10 being disease-free, 6 of whom had undergone graft nephrectomy .

The IPITTR data [58], compiled from voluntary reports of transmissions, conflict with those reported in the 2007 UNOS review [26]: in 140 transplants with grafts from donors with a past history of melanoma, only one transmission was reported (via a single lung). That donor had a melanoma resection 32 years before lung procurement and no transmission was reported from the other five recipients of grafts from the same donor. The analysed group of confirmed donor melanomas without transmission may

contain a mixture of melanoma stages, including cases of *lentigo maligna/in situ* melanoma. This might explain the low transmission rate in this analysis. The report does not preclude the existence of risks, but it concludes that improved data collection, with a description of the different stages of the donor melanomas, may help to clarify the issue. *Lentigo maligna*, as an *in situ* melanoma, must be distinguished from invasive melanoma for each individual case in order to determine whether this early stage should be considered separately from invasive melanoma.

In most published reports of donors with a known history of melanoma, the precise data about staging, therapy and follow-up are missing [26, 42, 58]. It has to be kept in mind that in non-transplanted patients malignant melanoma often recurs, even after many years of disease-free survival.

Alsara and Rafi [94] and Sepsakos *et al.* [95] reported the same donor-transmitted melanoma after ocular limbal stem-cell transplantation from a donor with a history of metastatic melanoma. Non-ocular malignancy had not been a contraindication for ocular tissue procurement in the USA in the past, except for leukaemia and lymphoma. After this case, the Eye Bank Association of America updated their donor criteria to exclude donors with *any* history of melanoma or other solid organ metastatic tumours from vascular ocular tissue donation (scleral tissue and keratolimbal allografts). Donors with known metastatic melanoma are excluded from any ocular tissue donation [96, 97]. The European Eye Bank Minimal Medical Standards also differentiate vascular from avascular tissue donation and have restrictions on donors with a history of malignancy for vascularised tissue donation [98].

Evidence increasingly indicates that single malignant melanoma cells spread to distant sites quite early during cancer progression. They can stay dormant and clinically undetectable after resection of the primary tumour for decades. To keep them dormant, a complex and fluctuating interaction between cells and environment is assumed. A change of this environment, e.g. transplantation of an organ with dormant melanoma micrometastases into a new and immunosuppressed host, can lead to metastatic growth in the recipient [99-101].

Late recurrences have been reported in non-transplanted patients with small melanomas < 1 mm in thickness [102], but are uncommon. Some yet unpublished cases, in which organs have been transplanted from donors with melanoma (mostly superficial spreading melanoma, SSM) stage pT1a No Mo (< 1 mm thick, non-ulcerated), resected (Ro), with recurrence-free survival > 5 years, are currently under evaluation.

Non-cutaneous, uveal melanoma tends to micrometastasise very early (before enucleation), and often to the liver [103, 104], where it may stay clinically undetected for years.

Because of the lack of data on tumour stage where donors with a history of melanoma have been used, and the tendency for melanoma metastases to lie dormant in an immunocompetent host, the utmost caution is recommended when considering donors with a history of melanoma [93], unless the tumour can definitely be confirmed as *lentigo maligna* or *in situ* tumour and curative therapy has been adequate [69]. For invasive cutaneous melanoma, Stage 1a (Breslow depth < 1.0 mm) tumours are associated with a melanoma-specific survival of around 95 % at 10 years [105], and around 98 % for tumours with a Breslow depth less than 0.8 mm (T1a) [106]. In all cases of melanoma, it is essential to obtain complete data about staging (including depth of invasion and ulceration), therapy, type of follow-up and recurrence-free duration, and then evaluate risk of metastasis with a dermato-oncologist before considering the case for donation.

Although transmission is often fatal, treatment options are emerging. Checkpoint inhibitors have been described in three cases, ideally following withdrawal of immunosuppression, graft rejection and then graft nephrectomy. In one case nephrectomy was undertaken before immunosuppression withdrawal following identification of melanoma in the liver recipient; widespread metastatic disease was found 3 months later, which was treated by resection of brain metastases followed by cranial irradiation and ipilimumab [89]. In the second report a metastatic melanoma exhibiting the BRAF-V600E mutation was found in a kidney recipient 6 months post-transplant. Following nephrectomy they were treated with trametinib and dabrafenib, followed by nivolumab with continuing tumour regression 14 months later [107]. The third report was also of a kidney transmitting metastatic melanoma (also BRAF-V600E mutation) treated successfully with vemurafenib, followed by ipilimumab, with complete remission at five years [92]. Successful treatment has also been reported using donor targeted immunotherapy [108].

Malignant melanoma diagnosed during donor procurement

Due to the very aggressive behaviour of this tumour, it is considered an unacceptable risk for organ donation.

Malignant melanoma in the donor history

Due to the lack of exhaustive data, transplanting organs from donors with treated malignant melanoma must still be considered to be associated with a high transmission risk. If precise donor data about staging, therapy, follow-up and recurrence-free survival are available, and evaluation by the dermato-oncologist concludes there is a low probability of recurrence and metastasis, organ donation might be considered for selected recipients.
In situ melanoma and lentigo maligna are considered low-to-intermediate risk for transmission.

9.4.15. Non-melanoma skin cancer

Basal cell carcinoma and squamous cell carcinoma of the skin usually do not metastasise and their existence in the donor history or diagnosis at procurement should therefore confer only minimal risk of transmission to the recipient. No reports exist of transmission of these tumours via organ transplantation.

In contrast, Kaposi sarcoma, Merkel cell carcinoma and skin sarcomas are very aggressive skin tumours. Patients with these diagnoses, whether at procurement or in their history, are not acceptable as organ donors.

For recommendations regarding non-melanoma *in situ* skin cancer, refer to section 9.4.7.

Non-melanoma skin cancer diagnosed during donor procurement or in donor history

Basal cell and squamous cell carcinoma of the skin are considered minimal risk due to very rare metastases. Kaposi sarcoma, Merkel cell carcinoma and skin sarcoma are considered an unacceptable risk.

9.4.16. Neuro-endocrine tumours

This section refers to high-grade neuro-endocrine carcinoma (NEC), low-grade neuro-endocrine tumours (NETs), phaeochromocytoma (PCC) and paraganglioma (PGL).

NEC and NETs most commonly arise in intestinal, lung or pancreatic tissue, but can be detected anywhere.

Transmission of previously unknown donor NEC has been reported [83, 84, 109-114]. All these tumours were high-grade (small-cell) NEC, two of which exhibited paraneoplastic adrenocorticotropic hormone (ACTH) production [84, 109], with kidney recipients typically presenting at around 12 months, while liver recipients presented around 4 months post-transplant. All these tumours showed aggressive behaviour that frequently led to death. One liver recipient underwent successful retransplantation 5 years post-transplant, having had the NEC followed since day 11; he was alive 12 months later [114]. Retransplant was attempted in two other liver recipients, but both died from extra-hepatic metastases [111, 112]. Five kidney recipients are alive after graft nephrectomy and chemotherapy [84, 109], with two still receiving chemotherapy at the time of reporting [83, 110]. Therefore, in cases of confirmed NEC transmission, all recipients of organs from the same donor should be considered for immediate retransplantation of the liver or transplant nephrectomy after immunosuppression reduction.

No data exist on the risk of transmission of well-differentiated NET (e.g. carcinoid tumours) following transplant.

Because of the impossibility of definitely excluding micrometastases during organ procurement, newly detected high-grade NEC should be a contraindication for organ donation.

PCC and PGL are catecholamine-secreting tumours of the adrenal medulla and extra-adrenal regions, respectively. Approximately 10 % of PCC and 15-35 % of PGL behave in a malignant fashion. At present the only accepted criterion for malignancy is the presence of metastases. Late metastases have been reported up to 20 years after initial tumour resection [115]. In the absence of lymph node or distant metastases (lungs, bone, liver) at the time of the diagnosis, it is not possible to determine whether the tumour is benign or malignant. Factors associated with malignant behaviour include male gender, extra-adrenal location, greater tumour weight (average 383 g for malignant *v.* 73 g for benign), confluent tumour necrosis, vascular invasion and extensive local invasion [116]. Thompson [117] developed a system for assessing malignancy of PCC, the PASS score (Phaeochromocytomas of the Adrenal gland Scaled Score), which analyses and scores vascular invasion, mitotic index (> 3), diffuse growth, diffuse necrosis, local invasion and nuclear atypia. Although all these features are possibly correlated with a potential malignant behaviour, the high inter- and intra-observer variations limit the clinical use of this score.

It is extremely difficult to predict the biological behaviour of these tumours when first detected during organ procurement. Criteria such as size and weight of the tumour mass, presence of necrosis, high mitotic rate and infiltrative margins can help to identify the risk profile for transmission, but the mitotic index in particular may not be assessable by frozen section. Elevated metanephrine levels in urine or plasma in a potential organ donor with a history of PCC/PGL require further evaluation to exclude metastasis.

PCCs and PGLs are rarer in the paediatric population than in adults, but the chance of malignancy is higher among children with these tumours, with a reported incidence of 47 % [118].

One single case report describes a kidney transplant from a donor with a PCC found intraoperatively. Due to the suspected non-malignant behaviour of the tumour, kidney transplantation was performed and the recipient of the ipsilateral kidney was well 2 years thereafter [119]. The contralateral kidney recipient died of tumour-unrelated causes shortly after transplantation.

One case of transmission of PGL has been reported, with donor tumour discovered in a transplanted liver 6 years post-transplant following presentation with signs attributable to excess production of catecholamines; the donor had been noted to have a 3 cm necrotic mass near the aortic bifurcation, the histology of which was of PGL [120, 121].

Careful risk–benefit consideration is necessary in individual cases of PCC and PGL.

Neuro-endocrine tumours diagnosed during donor procurement

Due to their potential for undetected metastasis, high-grade neuro-endocrine carcinomas are an unacceptable risk for organ donation.
Insufficient information exists to guide practice for neuro-endocrine tumours, carcinoid tumours, PCCs and PGLs. In the case of critically ill recipients, these tumours might be acceptable after a careful individual risk–benefit analysis.

Neuro-endocrine tumours in the donor history

No data are available from the literature. Due to this and their potential for undetected metastasis, treated high-grade neuro-endocrine tumours in the donor history are classified as high risk for organ donation.
In the case of a previous history (> 5 years) of neuro-endocrine tumours (carcinoid tumours, PCCs and PGLs) without any kind of disease recurrence or progression, donors should be considered high risk in the absence of sufficient information to guide practice.

9.4.17. Oesophageal, gastric, intestinal, pancreatic, liver and biliary cancers

For the majority of these tumours, only scarce data are available. There are two reported liver transplants from donors with confirmed oesophageal carcinoma without transmission [39], but no information about initial stage and recurrence-free survival of the donor is provided. No transmission of oesophageal cancer has been described in the published literature so far. This might be a reporting bias and should not lead clinicians to freely accept organs from donors with such aggressive tumours.

Regarding gastric cancer, there is one case report [122], in which pre-donation evaluation of a living liver donor revealed early gastric signet cell cancer (pT1NoMo, sm1). The designated recipient was the 9-month-old child of the living donor and there was no other living or deceased donor available; meanwhile the child's health was deteriorating rapidly. One month after gastrectomy in the donor, liver donation and transplantation were performed. Donor and recipient were well and without malignant disease one year thereafter. This example illustrates an extraordinary situation and should not justify such procedures as a good or routine practice.

In a donor screening programme in Italy, 0.7 % of donors were found to have a pancreatic adenocarcinoma [41]. Transmission of an undetected pancreatic adenocarcinoma through kidney transplantation has been reported in one case [123]. The tumour was diagnosed after the kidney had been transplanted (in the adrenal tissue that was removed during bench preparation). The recipient developed pulmonary lymphangitis carcinomatosa nine months after transplantation and died six months later. Another transmission of pancreatic carcinoma was detected 12 months after transplant in a liver recipient who underwent retransplantation and was alive at the time of the report [25]. Three further recipients have suffered from transmitted pancreatic cancer, details of which have not been reported [5]. One recipient has been reported with transmitted hepatocellular carcinoma [5].

One renal transplant patient in the series reported by Georgieva *et al.* [124] developed a donor-derived cancer that was found 4 months after transplant and suspected to be of biliary origin. Two other recipients of the contralateral kidney and the liver from the same donor, who had an unremarkable medical history, also developed metastatic adenocarcinoma, whereas no tumour was found in the heart or pancreatic islet recipients. No other reports of suspected or proven transmission of biliary cancer are available in the literature. For recommendations regarding *in situ* pancreatic cancers go to section 9.4.7.

Pancreatic intra-epithelial neoplasia (PanIN), grades 1-3, represents a non-invasive precursor lesion to pancreatic adenocarcinoma with cellular atypia, but without risk for metastases. PanIN do not form a mass, and are frequently associated with chronic pancreatitis. In the context of organ donation, PanIN will be found in three circumstances. First, they may occur in a donor who has previously had an abnormal lesion biopsied. These are often at the edge of frankly

malignant tumours, so full histological examination of the lesion will be necessary. Second, they may be detected during organ procurement as part of a palpable abnormality, and third, PanIN may be detected incidentally in the histopathological examination of a non-transplanted pancreas. In the absence of any data, transplantation of the pancreas with known PanIN is not recommended.

An analogous situation of preneoplastic change occurring in the larger intrahepatic bile ducts is known as biliary intra-epithelial neoplasia (BilIN) and is graded similarly [125]. In the absence of any data, transplantation of a liver with known BilIN is not recommended.

Yamacake *et al.* [75] reported the transmission of a metastatic intestinal adenocarcinoma, undetected in the donor, into both kidney recipients. This indicates the existing risk of tumour transmission through organs which are not considered to be the primary target of metastases.

Oesophageal, gastric, pancreatic, liver and biliary cancers diagnosed during donor procurement

These tumours are classified as unacceptable risk.

Oesophageal, gastric, pancreatic, liver and biliary cancers in the donor history

Treated tumours of these kinds in the donor history are classified as high risk due to their aggressive behaviour. Risk may decrease for early stages after curative therapy, with recurrence-free time > 5 years and with increasing probability of cure, especially in cases of long-term survivors.

9.4.18. Oropharyngeal cancer

A pyriform sinus carcinoma which manifested in the kidney recipient as liver metastases was reported by Murray *et al.* in 1965 [1]. No further reports of transmission are available from the literature. There is a report of 11 organs transplanted from donors with a history of tongue/throat cancer, without transmission. The initial tumour stage was not reported but all recipients had a recurrence-free survival of > 5 years [26]. However, the aggressiveness of these tumours should be kept in mind.

Oropharyngeal cancer diagnosed during donor procurement

The presence of oropharyngeal cancer is considered an unacceptable risk for organ donation.

Oropharyngeal cancer in the donor history

Treated oropharyngeal cancer is considered high-risk for organ donation. Depending on initial stage, grade, therapy and time of recurrence-free survival (> 5 years), the risk category might decrease individually.

9.4.19. Ovarian cancer

There is one published case report [126] about transmission of ovarian cancer into two kidney recipients, with fulminant metastatic disease leading to recipient death.

Nickkholgh *et al.* [127] reported a potential donor with a past history of well-differentiated serous ovarian carcinoma. The tumour had been treated surgically and there was no evidence of disease for a 10-year period. At the time of organ procurement, a pelvic recurrence of the tumour was identified and the organs were not used. This highlights the need for meticulous inspection in the setting of a positive cancer history.

UNOS reported three donors with possible but not proven transmission of ovarian cancer, the details of which are not reported [30]. Beyond these reports, there are no further data available in the literature.

In contrast, Desai *et al.* [35] reported two donors with mucinous cystadenomas treated 11 and 14 years previously, from which organs were transplanted with no cancer transmission

Ovarian cancer diagnosed during donor procurement

Ovarian cancer is considered an unacceptable risk for organ donation.

Ovarian cancer in the donor history

Treated ovarian cancer is considered high-risk for organ donation. Depending on initial stage, grade, therapy and time of recurrence-free survival (> 5 years), the risk category might decrease individually.

9.4.20. Pancreatic cancer

See section 9.4.17.

9.4.21. Pancreatic intra-epithelial neoplasia

See section 9.4.7.

9.4.22. Paraganglioma

See section 9.4.16.

9.4.23. Phaeochromocytoma

See section 9.4.16.

9.4.24. Prostate cancer

Given the increased incidence of prostate cancer with advanced age and the increasing age profile of donors, it is certain that organs from donors with undiagnosed prostate cancer are currently being utilised.

Sánchez-Chapado *et al.* [128] evaluated prostate cancer in a consecutive series of prostate glands collected at *post mortem* examination from 162 Spanish males who died from trauma. They reported prostate cancer in 23.8 % of individuals aged 50-59 years, 31.7 % aged 60-69 years and 33.3 % aged 70-79 years.

Yin *et al.* [129] found incidental prostate adenocarcinomas in 12 % (41/340) of presumed healthy organ donors over a 13-year period with a similar frequency (23.4 % aged 50-59 years, 34.7 % aged 60-69 years, 45.5 % aged 70-81 years).

In Italy, digital rectal examination (DRE) of male donors over 50 years is mandatory [13], and is combined with assay of prostate-specific antigen (PSA) in order to assess the need for histological examination of the prostate:

- negative DRE with PSA < 10 ng/mL: histological examination of the prostate is not required;
- negative DRE but PSA values > 10 ng/mL: histological evaluation preferred but not mandatory;
- positive DRE: histological examination is mandatory.

There is broad consensus that single PSA testing alone is not of high prognostic value [130]; moreover, there is no agreement as to what PSA levels should be considered suspicious or even normal. PSA should be measured on the first blood sample after admission, if available, because its value is influenced by catheterisation.

Pabisiak *et al.* [131] reported that the application of PSA screening to the Polish donor population resulted in a 10 % disqualification rate for male donors when a cut-off of > 10 ng/mL was used. They performed follow-up analysis by routine pathologic evaluation of prostates from all male donors over a 4-year period and were unable to find any correlation between elevated (> 4 ng/mL) PSA and either prostate carcinoma or high-grade prostatic intra-epithelial neoplasia. During this study, 12 kidneys and three livers from donors with prostate cancers that were histologically confirmed and confined to the prostate were transplanted with no evidence of disease transmission during 9-52 months of follow-up. A second report from another Polish centre made similar observations that potential liver donors were being disqualified unnecessarily [132].

For confirmed prostate cancer, the Gleason score [133] and the corresponding grading group according to the ISUP WHO 2014 system [134] in conjunction with staging are the strongest predictors for clinical recurrence and overall survival. For practical purposes, prostate cancers are generally classified by grade groups according to Gleason's score, each with significant differences in outcome (higher scores/groups result in poorer outcomes). The score represents tumour grade, with 1 being well differentiated and 5 the most poorly differentiated. The first number represents the predominant pattern, and the second number the second most predominant pattern. The following overview is describing the recurrence risk in non-transplant patients with prostate cancer:

• Grade Group 1	Gleason ≤6 (e.g. 3 + 3, or 3 + 2, etc.)
• Grade Group 2	Gleason 3 + 4
• Grade Group 3	Gleason 4 + 3
• Grade Group 4	Gleason 4 + 4
• Grade Group 5	Gleason 4 + 5, 5 + 4, 5 + 5

Group 1 tumours are associated with low risk of biochemical recurrence, groups 2 and 3 with intermediate risk and group 4 and 5 with high risk. The presence and the amount of Gleason patterns 4 and 5 are the strongest histological predictors of prostate cancer aggressiveness and local or distant relapse [18].

In the non-transplant setting, carefully selected, very low-risk patients with localised small prostate carcinomas T1/2 and Gleason score 3 + 3 may be followed with an 'active surveillance' approach [135], meaning that they will not undergo surgery but are surveyed at short intervals for further disease progression, since the rate of disease progression is slow and the morbidity from treatment (surgery, radiotherapy or hormonal treatment) is significant. In the ProtecT study of different treatment strategies, 920 patients in Grade Group 1 underwent active monitoring of whom 31 (3.4 %) developed metastases or died from prostate cancer during the 10 years of follow-up; 24 (14.3 %) of 168 in Group 2 and nine (19.1 %) of 47 in Group 3 also developed metastases or died from prostate cancer during follow-up [136].

The importance of Grade Group is acknowledged in the study of Pabisiak *et al.* [131], who concluded that donors with tumours confined to the prostate and with Gleason scores of 7 or less could be considered as standard-risk donors, although the data from ProtecT would suggest a score of 7 entails a slightly higher risk.

In 2010, the Emilia-Romagna Region and the Italian CNT published the results of a 4-year experience in donors with suspected prostate cancer, eval-

uating the entire gland with frozen sections [137]. According to the initial risk classification, donors were classified for transmission risk into three categories:

- no prostate cancer or intra-prostatic tumour with a Gleason score ≤ 6 – *standard risk* (2015 classification: *Non-standard – negligible risk*);
- intra-prostatic tumour with a Gleason score 7 – *non-standard risk* (2015: *Non-standard – acceptable risk*);
- pT3a/b extra-prostatic cancer or lymph nodes and/or distant metastases – *unacceptable risk* (2015: *Unacceptable risk*).

The Italian guidance also required an expert second opinion.

Overall, 94 % of the donors with suspected prostate cancer were classified as standard-risk, compared to 63 % in the period before implementation of this protocol. A significant increase in the number of transplanted organs was achieved by expanding the criteria for standard-risk donors.

An updated report from Italy in 2019 covering the period 2006 to 2015 described 112 (26.5 %) donors with prostate cancer out of 422 donors with malignancy [41]. No transmission has been reported from previously known tumours after a mean follow-up time of 4.5 years of all transplanted recipients (97 % return rate).

OPTN/DTAC reported five autopsy-proven cases of donor prostate adenocarcinoma without evidence of transmission [5]. A review by Doerfler *et al.* [138] documented 120 organ transplants from donors with confirmed prostate cancer with no evidence of disease transmission.

Additionally, a meta-analysis of the literature on kidney transplantation from donors with prostate cancer by Dholakia *et al.* [139] states that the risk of transmitting prostate cancer is lower than the risk of remaining on the waiting list. Acceptance of these donors requires careful donor characterisation and selection.

While most donors with prostate cancer have low Gleason grade disease, with minimal transmission risk, two cases of prostate cancer transmission have been published, one in the context of heart transplantation in 1997 [140] and one with liver transplantation in 2019 [141].

The heart donor was found to have prostate adenocarcinoma metastatic to lymph node and adrenal gland at the time of donation [140], but only after the donor heart had been procured and the recipient heart explanted. This case is referred to in various registry reports [4, 25, 32].

In the second case, three nodular lesions were detected in the hepatic allograft two months after transplantation [141]. The biopsy showed a well-differentiated adenocarcinoma of probable prostatic origin. In the absence of any prostatic tumour pathology of the recipient, hormone- and chemotherapy initially stabilised the patient. Donor origin of the prostate cancer metastases was finally proven by molecular testing after hemi-hepatectomy three years later. Shortly after, additional peri-oesophageal lymph node metastases were found.

Prostate cancer diagnosed during donor procurement

If Gleason score is available, e.g. prostate diagnostics have been initiated a few days before organ procurement, then small intra-prostatic, low-grade (Gleason score ≤ 6) tumours are considered minimal-risk; intra-prostatic tumours with Gleason score 7 are considered low-to-intermediate risk; and intra-prostatic (pT2) tumours with Gleason score > 7 are considered high-risk.
Histological examination of the entire prostate with a valid grading of the tumour is time-consuming and the results might not always be available before an organ is transplanted.
Donors with extra-prostatic tumour extension should be unequivocally excluded from the donation process as an unacceptable risk.

Prostate cancer in the donor history

The acceptable time intervals for complete remission of prostate cancer are strongly correlated with stage and Gleason grade of the tumour.
Donors with a history of curatively treated prostate cancer ≤ pT2 (tumour confined to prostate) and Gleason 3 + 3, as well as donors with very small prostate cancers and Gleason 3 + 3 under 'active surveillance', can be accepted for organ donation as minimal transmission risk at any time after diagnosis with the prerequisite of a frequently performed and non-suspicious follow-up.
Prostate cancer ≤ pT2 (confined to the prostate) and Gleason grade < 7 after curative treatment and cancer-free period > 5 years is considered minimal-risk.
Higher stages/grades and/or shorter cancer-free periods require an individual risk assessment. A history of extra-prostatic tumour extension poses a high risk for transmission.
In these cases of past prostate cancer, current PSA values should be obtained to compare to former ones in order to assess the likelihood of dissemination.

9.4.25. Renal cell carcinoma

RCC is the most common cancer encountered in deceased donors. The literature on RCC and transplantation covers four general topics:

- inadvertent transplantation of kidneys that contain RCC not recognised at the time of operation;
- resection of a small RCC at time of procurement with subsequent transplantation of the kidney;
- transplantation of contralateral non-cancerous kidneys or other organs from donors with solitary renal cancers and
- donors with a history of RCC.

9.4.25.1. *Renal carcinoma not recognised at the time of transplantation*

In 1995, Penn [3] published the first report on donors with RCC, describing the use of two kidneys with RCC at the time of transplant, eight where the RCC was widely excised before implantation, 14 where the contralateral kidney was used and 17 where RCC became apparent in the kidney soon after transplant. Both recipients who received kidneys with unresected active tumour died with evidence of metastatic disease. Of those 17 recipients where RCC was not recognised at the time of transplant, nine had the kidney removed early post-transplant due to other complications (8 RCC, 1 urothelial tumour) or following donor autopsy findings of disseminated RCC (n = 2). In a further case the kidney was removed 2 years later for urothelial cancer with no recurrence at least 13 months post-nephrectomy. The seven remaining patients died from metastatic disease an average of 12 (range 3-47) months post-transplant.

OPTN/DTAC [5] described seven recipients with confirmed transmissions from 64 donors with RCCs, while Desai *et al.* [6] described six transmitted RCCs incidentally detected in protocol biopsies or biopsies to assess graft dysfunction. The recipients of other organs of those donors were tumour-free. In a recent systematic review of donor cancer transmission by renal transplantation, Xiao *et al.* [71] found 20 examples of RCC transmission. In each case the presence of tumour was not known by the surgeons at the time of transplantation.

9.4.25.2. *Resection of a small RCC at time of procurement, with subsequent transplantation of the kidney*

Nephron-sparing surgery is an established curative approach for the oncological treatment of RCCs ≤ 4 cm (pT1a) in the non-transplant population [142] with cancer-specific survival rates comparable to radical nephrectomy [143]. However, it should be remembered that, in the oncology setting, pre-operative imaging would have staged the cancer, something that is possible in a living donor setting but not in a deceased donor.

A number of reports demonstrate successful outcomes when small (pT1a, ≤ 4 cm), solitary and well-differentiated (Fuhrman grade I-II) RCCs have been resected at time of procurement followed by transplantation of the treated kidney [3, 6, 8, 9]. In a recent systematic review of such cases, Hevia *et al.* [144] reported 88 kidneys with RCC that had undergone resection before transplantation, including 51 clear cell, eight papillary and three chromophobe carcinomas; in 26 cases the type of RCC was not reported. The mean tumour size was 2 cm and Fuhrman grade was I or II in 93 % of cases. There was one recurrence of cancer at nine years remote from the cancer resection site which was more likely a donor-derived than donor-transmitted cancer. The majority of donors in this review were living donors. In 2014, a systematic review by Yu *et al.* [145] found 20 examples of kidneys transplanted after resection of well-differentiated (and one Fuhrman grade III) RCC at the time of procurement, with some overlap with cases later reported by Hevia *et al.* Tumour sizes ranged from 0.5 to 4 cm in size with follow-up times up to 200 months. No tumour transmission occurred.

In 2019 Pavlakis *et al.* [146] reviewed all RCC cases reported to OPTN/DTAC between 2008 and 2016. Of the 26 cases where tumour was resected before transplantation, five were in living donors, most were Fuhrman I or II with one grade III, and all were ≤ 2.1 cm (pT1a); the reported tumour types included 14 clear cell, seven papillary and one combined clear cell/papillary carcinoma. There was no recurrence.

Following a review of the literature in 2011, the UNOS DTAC [8] concluded that solitary well-differentiated (Fuhrman grade I or II) RCCs less than 1 cm and completely resected prior to transplant were associated with a minimal residual risk of transmission, while those of 1-2.5 cm carried a low risk and those of 2.5-7 cm carried an intermediate risk of transmission. Large tumours ≥ 7 cm were considered high-risk. However, in spite of their recommendations, there is absence of data to support the safe use of kidneys with resected tumours over 4 cm.

Many of the reports of resected tumours are in a live donor setting, some during planned live donor operations [147] and others as part of a therapeutic nephrectomy for cancer [148, 149]. Ethical considerations have been raised regarding donation after therapeutic nephrectomy in such circumstances [150]; indeed the American Society of Clinical Oncology guidelines recommend offering partial nephrectomy

as treatment for patients with small renal cancers that are amenable to this approach [151].

9.4.25.3. *Transplantation of contralateral non-cancerous kidneys or other organs from donors with solitary renal cancers*

The tendency of renal cancers to metastasise is a function of size and grade. In a study of 1 671 patients undergoing therapeutic radical nephrectomy for a primary clear cell renal cancer, Leibovich *et al.* [152] showed that the 5-year recurrence-free survival of a patient with a pTa (< 4 cm) tumour of Fuhrman grade III or less was 98.7 %. For a pT1a grade IV it fell to 78.6 %, while a pT1b (4-7 cm) grade I or II tumour had a 5-year recurrence-free survival of 95.3 %, falling to 78.6 % for a grade III cancer.

In 1995 Penn [3] reported 14 cases where the contralateral kidney was transplanted, with tumour-free survival at an average of 55 months (range 0.5 to 153), but with one transmission found in a kidney explanted for rejection at 3 months. No details of tumour type were reported.

In the recent OPTN registry report there were 47 donors from whom the contralateral kidney was transplanted, together with 198 non-renal organs with no report of transmission [146].

Between them, Serralta *et al.* [153] and Carver *et al.* [154] reported five donors with RCC from whom five livers and one contralateral kidney were transplanted with no recurrence at a median 55 (range 14 to 68) months.

The ONT Registry did not detect any tumour transmission among 56 recipients transplanted with grafts from 47 donors registered with RCC (15 kidneys, 29 livers, seven hearts and five lungs). Prophylactic removal of the graft was performed in nine of these kidneys, two livers and one heart. After 3 years of follow-up, tumour transmission had not appeared in any of the cases. As mentioned in section 9.3.1.5, in two of the cases a kidney with an occult tumour had been transplanted. Here, the incidental diagnosis was made by biopsy after transplant and was followed by transplant nephrectomy; no symptomatic malignancy was observed.

The MALORY initiative [9] described a 6-year experience with the transplantation of organs from 35 donors with RCC (three in donor history, 20 found at organ procurement, 12 diagnosed before implantation). From these donors 28 livers, 18 kidneys, 13 hearts and 13 lungs were transplanted, though the affected kidneys were not accepted. No tumour transmission was reported after 2 years. In parallel, three further donors had an occult RCC at the time of transplantation. These RCCs were diagnosed incidentally after transplant nephrectomy for tumour-unrelated causes 6-46 days after transplantation. The recipients did not show any symptomatic malignancy.

In contrast to the favourable reports above, Meyding-Lamade *et al.* [155] and Sack *et al.* [156] reported separate cases of transmission of a donor RCC which had been detected at the time of procurement during the ongoing transplantation of the heart; both recipients presented one year post-transplant with focal neurology secondary to intracranial metastases; they subsequently died. Details of the type and grade of renal tumour in each case are not known.

Barrou *et al.* [157] described transmission of an RCC to recipients of a heart and contralateral kidney. A 17 mm tubulo-papillary adenoma Fuhrman grade I-II (classified as carcinoma according to current standards) had been detected under the peri-nephric fat after transplantation of the other organs. The contralateral kidney recipient underwent a transplant nephrectomy 4 months later due to tumour infiltration of the kidney, while the heart recipient died 7 months after transplantation due to metastatic renal cancer. At that time the tumour was described as being undifferentiated, raising the possibility that it may have been unrelated to the original small, well-differentiated tumour. Furthermore, the tumour grew in an infiltrative pattern, which is unusual for RCC.

Yu *et al.* [145] reviewed reports of 21 contralateral healthy kidneys from donors with RCC. Except for the transmission case of Barrou *et al.* [157] described above, there were no reported transmissions from those kidneys.

Buell *et al.* [32] reported two donor RCCs that were metastatic at the time of procurement (detected after transplantation of organs) that were transmitted in lung and heart/lung recipients who both died of metastatic disease. Organs from three further donors with RCCs, detected during procurement and confined to the kidney, were transplanted without transmission, with a follow-up of 30, 36 and 70 months.

9.4.25.4. *Donors with a history of renal cancer, including Wilms tumours*

In contrast to the reports of cancers found at the time of donation, there are few reports of donors with a past history of renal cancer. In particular, there are no reports of donors who have previously had a Wilms tumour (nephroblastoma) as a child. Wilms tumours are bilateral in 10 % of cases, and usually present before the age of 5. Following nephrectomy and chemotherapy 90 % of children survive 5 years, with recurrence usually occurring in the first two years [158].

9.4.25.5. *Assessment and interpretation of renal masses*

Assessment of renal masses at time of procurement should include histological analysis since in some cases benign conditions (e.g. oncocytoma, adrenal rest, angiomyolipoma) can mimic RCC. In addition to providing a diagnosis, the histology report in the case of RCC should comment upon the size of the resected lesion (if only a biopsy is taken, the surgeon should provide the size of the lesion), estimate of WHO/ISUP grade (which superseded Fuhrman grade) and adequacy of resection margin. Typing of renal tumours is difficult on frozen sections, unless obviously a clear cell or papillary RCC, so a rapid paraffin section is preferable where possible. A rapid paraffin section is also necessary for grading a clear cell RCC.

The 2016 WHO/ISUP grading system for RCCs [159, 160] is based on the assessment of the nucleolar grade (grades 1-4) and has been shown to be superior to Fuhrman grade for both clear cell and papillary RCCs [161, 162].

According to the 2016 WHO/ISUP classification of genito-urinary tumours, papillary renal neoplasms < 1.5 cm in size must be considered as benign papillary adenomas by definition [163] unless the analysing pathologist finds evidence for malignant behaviour. Borderline cases should be discussed thoroughly.

RCCs can be multifocal and have a bilateral incidence in 5 % of cases [164]. Careful examination and the use of ultrasound analysis are desirable for the identification of this tumour in both kidneys after removal, especially in the case of papillary RCC.

9.4.25.5.1. Oncocytic tumours

Oncocytic tumours are particularly problematic, even on standard histological assessment, as they usually require immunohistochemistry for typing [160]. On frozen section or rapid paraffin they would most likely be diagnosed as an 'oncocytic renal cell neoplasm'. This would include a range of neoplasms: benign oncocytomas, hybrid tumours, chromophobe RCCs. It is very difficult to give a confident diagnosis of a benign oncocytoma without immunohistochemistry.

9.4.25.5.2. Sarcomatoid and rhabdoid RCC

Llamas *et al.* [165] reported the transmission of sarcomatoid RCC in two kidney recipients after transplant without any evidence of tumour in the organs at the time of transplantation. Sarcomatoid morphology may occur in different types of RCC and confers a worse prognosis. This component, when present, is regarded as WHO/ISUP Grade 4 [160]. The rare purely sarcomatoid tumours are included in the 'unclassified' RCC category of the WHO 2016 classification. These are more aggressive than clear cell RCCs and typically are found to have metastasised at diagnosis. Rhabdoid morphology is also associated with poor prognosis, and its presence is classified as WHO/ISUP grade 4 [160]. Presence of rhabdoid or sarcomatoid features on a procurement biopsy would contraindicate the use of organs from such donors.

RCC diagnosed during donor procurement

To provide valid histological staging, complete tumour resection (R0) is required for acceptance of all organs; additionally, tumour-free margins are a prerequisite for transplantation of the affected kidney. Paraffin section is superior to frozen section for assessment of such biopsies. The contralateral kidney should always be examined for synchronous RCC (5 % of patients).

- ◊ RCC < 1 cm (stage T1a AJCC 8th edn) and WHO/ISUP grade 1/2 (Fuhrman grade I/II) can be considered minimal-risk for transmission;
- ◊ RCC 1-4 cm (stage T1a AJCC 8th edn) and WHO/ISUP grade 1/2I (Fuhrman grade I/II) are considered low-risk;
- ◊ RCC > 4-7 cm (stage T1b AJCC 8th edn) and WHO/ISUP grade 1/2 (Fuhrman grade I/II) are considered intermediate-risk;
- ◊ RCC > 7 cm (stage T2 AJCC 8th edn) and WHO/ISUP grade 1/2 (Fuhrman grade I/II) are considered high-risk;
- ◊ RCC with extension beyond the kidney (stages T3/T4 AJCC 8th edn) is considered a contraindication to transplant;
- ◊ All RCC with WHO/ISUP grade 3/4 (Fuhrman grade III/IV) are considered high-risk for transmission;
- ◊ Contralateral kidneys and other organs that are uninvolved in carcinoma are considered to represent minimal risk for transplantation when the RCC in the involved kidney is 4 cm or less and WHO/ISUP grade 1/2;
- ◊ The presence of sarcomatoid or rhabdoid features on histology is a contraindication to use any organs from the donor.

In all cases, follow-up surveillance is desirable.

RCC in the donor history

The transmission risk of treated RCC depends on the histological type of tumour [163] and its recurrence-free follow-up period. In general, in the first 5 years after initial diagnosis, risk categories correspond to those stated above (RCC diagnosed during donor procurement) if there is no suspicion of tumour recurrence in the donor. After this time, the risk of advanced stages may decrease.

9.4.26. Sarcoma

Despite a bewildering variety of sarcomas, guidance in most cases (with a few exceptions, e.g. GIST: see §9.4.1) is based on the fact that these tumours as a group tend to behave aggressively, with a propensity to recur and spread. Sporadic case reports document extended survival following early transplantectomy [32, 166, 167], but the usual outcome after transmission is fatal [7, 168, 169]. For this reason, sarcoma or a history of sarcoma is at present considered a contraindication to organ or tissue donation.

Kaposi sarcoma, related to transmission of HHV8, is discussed elsewhere. There are no reports of osteosarcoma and organ transplantation.

Sarcoma diagnosed during procurement

Due to the very aggressive behaviour of sarcomas, they are considered an unacceptable risk for organ donation at any stage of disease.

Sarcoma in donor history

Because of the very aggressive behaviour of sarcoma, it is mostly considered an unacceptable risk for organ donation. After curative treatment and a recurrence-free survival of > 5 years, sarcoma is still assumed to be associated with a high risk for transmission.

9.4.27. Squamous cell carcinoma of the skin

See section 9.4.15.

9.4.28. Testicular cancer

The UNOS registry report for the period 1994 to 1996 [23, 24] cited two kidney transplants from a donor who had testicular cancer treated within the preceding 5 years, with no recurrence; no further details were presented. In a follow-up publication from the same registry covering 2000 to 2005, 28 transplants were reported from donors with testicular cancer, including 14 kidney, nine liver, three heart and two lung transplants [26]. Most of the donors had been cancer-free for over 10 years, with just one donor within 5 years of treatment. Oerlemans *et al.* [170] report one case of a testicular teratoma diagnosed at retrieval during which it was found to have spread into the retroperitoneum. The heart explant had already progressed beyond the point of no return when the cancer was identified so the transplant proceeded; the recipient died from cancer transmission three months later.

Almost all non-transplant men with stage 1 testicular cancers (disease confined to testis) are ultimately cured, but clinical management may involve orchidectomy and surveillance, with treatment of relapse as opposed to prophylactic chemotherapy; around 15 % of patients with stage 1 seminoma and 20 % of non-seminoma testicular cancers will relapse [171], with alpha-fetoprotein (AFP) and beta human chorionic gonadotrophin (βHCG) tumour markers being used to assess disease status; these should be repeated before donation. Potential donors in the surveillance stage of follow-up need careful assessment and consideration.

Testicular tumour diagnosed during procurement

Testicular cancer diagnosed at retrieval is considered an absolute contraindication to donation.

Testicular tumour in donor history

Given the good treatment response of testicular tumours in general and stage 1 tumours in particular, a stage 1 tumour with at least 5 years recurrence-free follow-up is likely to be associated with minimal risk. For other stages a higher transmission risk should be assumed, but risk will decrease with recurrence-free time and increasing probability of cure.

9.4.29. Thyroid cancer

Although there is a greater understanding of the genetics and prognosis of differentiated thyroid cancer (follicular and papillary cancers) [172, 173], its relevance to transplantation is not clear. Vascular invasion on histological examination is associated with metastatic spread, and conversely small tumours confined to the thyroid without vascular invasion or capsular invasion tend to behave in a benign manner. Nondifferentiated thyroid cancers, such as medullary carcinoma and anaplastic carcinoma, behave much more aggressively and probably contraindicate organ donation.

Not all palpable thyroid nodules are cancer, and in the Italian Emilia-Romagna screening report, of 15 potential donors with thyroid nodules only two were thyroid cancers, neither of whom became organ donors [14]. In a follow-up from Italy five of 7 608 (0.07 %) potential donors were excluded because thyroid cancer was detected [15].

Penn [4] described the only case of proven thyroid cancer transmission, with the tumour confined to the kidney at the time of nephrectomy; the nature of the tumour and outcome are not described. In the 2011 OPTN report of potential malignancy transmissions between 2005 and 2009, there were seven donors cited with possible, but not confirmed, transmission of thyroid cancer [5]. The same database report for 2013 noted a further six possible thyroid cancer transmissions [30]. In contrast, Fiascheti *et al.* [40] reported three donors with an un-

specified thyroid cancer donating to five recipients without report of transmission, and Benko *et al.* [174] reported two liver donors with thyroid cancer, both with a tumour-free interval over five years, donating without transmission. A 2019 report from Italy covering the period 2006 to 2015 noted 28 donors with thyroid cancer, with no transmission [41].

The below-mentioned recommendations [8, 11] have been based on knowledge of the behaviour of differentiated thyroid cancers based on histological appearance (follicular *v.* papillary), size and grade.

Thyroid cancer diagnosed during donor procurement

Solitary papillary thyroid carcinoma < 0.5 cm is considered minimal risk and 0.5-2 cm is considered low to intermediate risk.
Minimally invasive follicular carcinoma < 1 cm is considered minimal risk and 1-2 cm is considered low to intermediate risk.
Newly diagnosed medullary and anaplastic thyroid cancers are an unacceptable risk for organ donation.

Thyroid cancer in the donor history

Treated, small, differentiated thyroid cancers (papillary and follicular) are acceptable, analogous to the above recommendations for newly diagnosed thyroid cancers. Curative therapy and adequate follow-up are assumed.
No recommendations exist for medullary and anaplastic thyroid cancer but, because of their aggressive clinical behaviour, they should only be accepted for organ donation, if at all, with the highest caution and after a long-term recurrence-free follow-up.

9.4.30. Urothelial carcinoma

Reports of transmission of urothelial carcinoma are uncommon, and such tumours usually arise from the renal pelvis/ureter accompanying the allograft kidney.

Huurman *et al.* [175] documented ureteric obstruction as the first symptom in their recipient, and a separate patient reported by Ferreira *et al.* [176] developed gross haematuria three months after transplant as the first indication of tumour. In this latter case, the patient died with metastatic disease, and a liver recipient from the same donor required retransplantation for a metastatic donor urothelial cancer that arose in the allograft and is separately reported by Backes *et al.* [177]; the liver recipient was still well four years post-retransplant.

One of two patients reported by Hevia *et al.* [178] was found to have a high-grade urothelial carcinoma of the renal pelvis with fat infiltration on routine sonography 14 months post-transplant. The patient underwent allograft nephrectomy and was free of tumour at 14 months follow-up.

Penn [3] reported metastatic transmission of two undetected donor transitional cell carcinomas into two kidney recipients, both of whom died of the tumour.

Mannami *et al.* [179] reported the transplantation of eight kidneys from living donors undergoing therapeutic nephrectomy for transitional cell carcinoma of stages pTa (n = 3), pT1 (n = 1), pT2 (n = 3), pT3 (n = 1); three were papillary and four non-papillary, but the eighth was not sub-classified. The tumours were resected back-table before implantation, and negative margins were confirmed in permanent section. One recipient (pT3) developed local recurrence after 15 months (tumour resection performed) and died of presumed primary lung cancer (with liver metastases), but metastatic urothelial cancer could not be ruled out. An update in 2012 noted that two additional recipients had died from causes unrelated to the cancer, and 10-year graft survival was 50 % [180]. This practice and the published reports were subsequently criticised on both ethical and technical grounds, with a suggestion that the resections were performed in the operating field and not on the back-table, without informed donor consent, and with falsification of operative records [181].

Urothelial cancer guidelines and prognosis scores distinguish non-muscle-invasive cancer (pTa, pTis, pT1) from muscle-invasive stages (> pT2).

In Italy, the recommendations for the suitability of organ donors consider newly diagnosed single low-grade and low-stage (G1-2, pTa/pT1) papillary urothelial cancers as well as high-grade *in situ* urothelial carcinoma (pTis) as negligible risk for transmission (corresponding to minimal risk in the Council of Europe recommendations). Conversely, multiple tumours (including pT1), high-grade, muscle-invasive urothelial cancer of the bladder, the ureters and the renal pelvis infiltrating kidney parenchyma are considered as an unacceptable risk for organ donation in Italy. However, other evidence suggests that high-grade pTis may be associated with more invasive tumour foci, may be multifocal, and represents a higher risk, certainly for renal transplants if not for other organs [182].

In general, the highly aggressive behaviour and potential multicentricity of these tumours has to be respected in any risk–benefit assessment.

Urothelial cancer diagnosed during donor procurement

No literature exists regarding newly diagnosed urothelial cancer and organ donation. Therefore, the highest caution is recommended, and the advice of an urologist may be sought in assessing the individual donor tumour transmission risk. National recommendations should be followed since they vary in accepting these tumours.

Urothelial cancer in the donor history

Strict follow-up must have been provided after primary diagnosis because these tumours may be multicentric and tend to recur, with a need for repeated cystoscopy and TUR-B, and for restaging. Kidney transplantation will be associated with increased risk, but this has not been classified in the literature yet.
After a disease-free interval > 5 years, the transmission risk of invasive urothelial cancer will depend on the probability of cure and has to be assessed individually before accepting a potential organ donor. No specific recommendations are available from the literature.
The non-muscle-invasive urothelial cancers, *in situ* urothelial cancer (pTis) and intra-epithelial papillary urothelial carcinoma (pTa/G1-2) – see AJCC, 8th edition [18] – are considered minimal risk for non-renal transplants. Renal transplants from these donors should be considered as a higher risk for transmission due to the often multifocal character of transitional cell cancers and the higher risk of cancer in the renal pelvis.

9.4.31. Uterus and uterine cervix cancer

With the exception of cervical dysplasia/carcinoma *in situ*, which is not associated with tumour transmission [42], no data are available from the literature regarding transmission of uterine and cervical cancer.

In situ carcinoma of the cervix is also known as cervical intra-epithelial neoplasia (CIN) grade III. Less severe forms such as mild or moderate cervical dysplasia are referred to as CIN grades I and II, respectively. Cytologic preparations use the terms low-grade squamous intra-epithelial lesion to correspond to CIN I and high-grade squamous intra-epithelial lesion to correspond to CIN II or III. Tumour transmission risk seems to be negligible for all forms of dysplasia and *in situ* carcinoma of the uterine cervix and many other sites, with no transmissions being reported.

Uterus or uterine cervix cancer diagnosed during donor procurement

The presence of invasive uterine or cervical cancers is considered an unacceptable risk for organ donation.

Uterus or uterine cervix cancer in the donor history

After a disease-free interval > 5 years, the transmission risk of invasive uterine or cervical cancers will depend on the probability of cure, and has to be assessed individually before accepting the potential donor; no specific recommendations are available from the literature.
Cervical carcinoma in situ (CINIII) is considered to be minimal risk for transmission.

9.5. Haematopoietic malignancies

9.5.1. Leukaemia, lymphoma, plasmacytoma and monoclonal gammopathies of undetermined significance

There are case reports about inadvertent transmission of lymphomas [183-186]. In a systematic review of donor-transmitted cancer in renal transplant recipients, Xiao *et al.* [71] found 15 examples of lymphoma transmission with a median presentation of 4 months after transplant. One of the 15 had metastatic disease at presentation and later died of the disease.

Rarely, unsuspected donor T-cell lymphoblastic lymphoma has manifested as acute lymphoblastic leukaemia (ALL) in the recipient [187] and, conversely, donor leukaemia has presented as a solid tumour (promyelocytic sarcoma) in an organ recipient [188]. Haematopoietic diseases should be handled with the greatest caution in the organ donation process and donors presenting with them should typically not be accepted due to the systemic spread of such diseases.

One patient with a high-grade lymphoma and successful stem-cell transplantation 4 years before organ donation was accepted as a liver donor in Germany. The liver recipient was without signs of malignancy 3 years after transplantation [9].

Currently, no further data are available on organ donors after human stem-cell transplantation in short- and long-term survival cases without relapse. In patients who are in remission and being treated with advanced protocols (without stem-cell transplantation), transmission of malignant clones cannot be excluded.

Sosin *et al.* [189] reported a donor-related peritoneal plasmacytoma 3 years after transplantation in the liver recipient, showing chimeric donor and recipient origin. No further literature exists regarding plasmacytoma in organ donors.

Leukaemia, lymphoma and plasmacytoma diagnosed during donor procurement

These cancers are classified as an unacceptable risk for organ donation.

Leukaemia, lymphoma and plasmacytoma in the donor history

Active (acute or chronic) leukaemia, lymphoma and plasmacytoma are an unacceptable risk for organ donation. Treated acute leukaemia and lymphoma after a definite disease-free interval of > 10 years may be considered for organ donation with an assumed high risk for transmission.

9.5.1.1. *Monoclonal gammopathies*

Monoclonal gammopathies of undetermined significance (MGUS) should be considered in the growing population of aged donors [190]. In particular, the risk of progression to multiple myeloma or related disorders (1%/year) should be evaluated. Risk factors for malignant progression are a non-IgG M-protein, M-protein concentration > 15 g/L, altered serum ratio of free light chains (κ/λ) and light chain proteinuria. In this context, electrophoretic analysis is helpful in suspected cases [190]. Cases should also be discussed with a haematologist and possibly be investigated further with a bone-marrow biopsy where possible. Donors with MGUS may cause donor-transmitted malignancies via passenger lymphocytes/plasma cells in solid organ recipients [191]. On the other hand, there are reports in the literature of kidney living donors with known MGUS at donation without evidence of progression in the recipients 36 and 42 months post-transplantation, respectively [192].

Monoclonal gammopathies of undetermined significance (MGUS) in the donor history

MGUS with accurate diagnosis and appropriate follow-up without progression to multiple myeloma or related disorders after a definite disease-free interval of 5-10 years may be considered for organ donation and may be assumed to pose a low risk for transmission.
It might be reasonable to accept an organ donor with a pre-diagnosed MGUS, especially in cases of confirmed MGUS without progression where the diagnosis has been confirmed years before.

9.5.2. Myeloproliferative neoplasms

Myeloproliferative neoplasms (MPN) [193, 194] are a group of chronic malignant diseases caused by dysregulated multipotent haematopoietic stem cells, mostly diagnosed beyond the age of 50 although around 20 % of cases are in patients below the age of 40.

In the following three MPN diseases, the clonogenic stem cells produce increased numbers of blood cells in the peripheral blood, which can cause (e.g. thrombo-embolic or haemorrhagic) complications:

- polycythaemia vera (PV) – all cell lines can be increased (mainly erythrocytes, but also leukocytes and platelets);
- essential thrombocythaemia (ET) – increased platelets;
- chronic myeloid leukaemia (CML) – increased leukocytes (functioning granulocytes) and platelets.

In the fourth disease of the group, the clonogenic stem cells cause a fibrosis of the bone marrow with consecutively decreased blood cells:

- primary myelofibrosis (PMF) – initially leuko-/thrombocytosis and immature blood cells in the peripheral blood, then anaemia, later pancytopaenia.

All of these diseases frequently present with spleno-/hepatomegaly. They can transform into an acute myeloid leukaemia (blast crisis) or myelofibrosis, which leads to the death of the patient. The symptomatic therapy is primarily intended to control disease symptoms and to avoid thrombo-embolic complications [195]. The only curative therapy is allogenic stem-cell transplantation (mainly for PMF but rarely also for selected patients with polycythaemia vera and essential thrombocythaemia).

MPNs are treated symptomatically and generally have a good prognosis. Nevertheless it should be kept in mind that these are chronic diseases, which are normally not curatively treated, and therefore they bear a risk for transmission by organ transplantation. Literature has not addressed this topic yet, so there is no evidence available for a valid estimation of the transmission risk. Clonogenic stem cells are mainly located in the bone marrow, but they also circulate in the blood and can accumulate in spleen and liver (and might be transmitted by liver donation). It is possible that the stem cells may adhere to vessel walls even after perfusion of the organs during procurement and may therefore be released in the recipient's blood during reperfusion. Due to the lack of reports and evidence, the transmission risk cannot be assessed and it is not known how a transmitted MPN would behave in an immunosuppressed recipient.

Myeloproliferative neoplasms diagnosed during donor procurement

Due to the current lack of literature on MPN and organ donation, the transmission risk cannot be assessed. Organs from these patients should only be accepted with the highest caution and only after consultation with an experienced haemato-oncologist. Results of the bone-marrow biopsy should be carefully evaluated.

A patient admitted with nonspecific but suspect symptoms like extensive thrombo-/erythro-/leukocytosis should be tested for specific oncogenes in blood and bone marrow ($CD34^+$ cells, BCR-ABL, JAK-2, V617F-mutation, MPL-mutation, Calretikulin-mutation) to distinguish an MPN from a simply reactive situation. Since this will take 2-3 working days, it might not be suitable in the context of organ donation.

Myeloproliferative neoplasms in the donor history

Due to the systemic and chronic character of these diseases and the lack of evidence on their behaviour in the setting of organ transplantation (and in the immunosuppressed recipient), their transmission risk cannot currently be assessed. Organs from these patients should only be accepted with the highest caution.

The following laboratory tests might be obtained to assess the actual situation of the pre-diagnosed MPN: complete and differential blood count, liver enzymes including LDH. Bone-marrow biopsy can help to rule out blasts at the time of donation.

Patients with spleno-/hepatomegaly need particular attention. An experienced haematologist should always be asked for an assessment.

It might be reasonable to accept an organ donor with a pre-diagnosed MPN for selected recipients, especially in cases of confirmed MPN without need for treatment or in cases where the diagnosis has been confirmed years ago and good therapy results were obtained. PMF seems to be more risky, due to a higher proportion of circulating blasts, and might bear an even higher risk for transmission.

9.6. Primary tumours of the central nervous system

Primary malignant tumours of the CNS represent up to 1.5 % of the causes of death in organ donors [36, 196]. Extraneural metastases from CNS tumours are rare but have been described, the most common sites being the cervical lymph nodes, bone, lungs, pleura, liver and lymph nodes in the thoracic and abdominal cavities [197, 198].

Extraneural dissemination of CNS malignancies implies that tumour cells have accessed the blood vessels once they have infiltrated the tissues outside the leptomeninges. Several factors have been related to the risk of extraneural dissemination of CNS malignancy [199]:

a. specific histological types and grade of malignancy;
b. peripheral intracranial location;
c. previous history of craniotomy or stereotactic surgery;
d. ventriculo-systemic or ventriculo-peritoneal shunts;
e. previous history of chemotherapy or radiotherapy;
f. duration of the disease and length of survival after surgical treatment.

There are examples of spontaneous dissemination to the cranial and cervical lymph nodes, and even distant metastases [200]. It is estimated that 10 % of tumour metastases occur without prior surgical intervention and even within 3-6 months of tumour diagnosis [200].

With respect to the histological type, the neuroectodermal tumours that metastasise with greatest frequency outside the cranial cavity are glioblastoma and medulloblastoma. Extracranial metastases have also been described for several types of glioma other than glioblastoma (i.e. various grades of astrocytoma, ependymoma and oligodendroglioma) as well as benign and malignant meningioma and germ cell tumours. In a series of 116 cases of extracranial metastases of CNS tumours, the most common primary tumour was glioblastoma (41.4 %), followed by medulloblastoma (26.7 %), ependymoma (16.4 %), lower-grade astrocytoma (10.3 %) and oligodendroglioma (5.3 %) [198].

9.6.1. Classification of central nervous system tumours

The World Health Organization (WHO) provides a comprehensive classification of CNS neoplasia (see Table 9.4), based on the specific cell type involved. Revised in 2016, the WHO classification provides a grading system (I to IV) for each type of tumour, depending on its biological behaviour. This WHO grade dictates the choice of therapy and predicts prognosis [19, 201]. The 2016 classification also includes genotypic information that correlates with tumour behaviour; however, most case reports of intracranial tumours and transplantation relate to the previous classification without genotypic information. In the 2016 revision the term *glioblastoma multiforme* was changed to simply *glioblastoma*, but information on different genotypes of glioblastoma was added. The transmission risks of different genotypes in organ donation remain to be established.

9.6.1.1. *Characteristics of the WHO grades of CNS tumours*

The main characteristics of WHO grades of CNS tumours are as follows.

- WHO grade I applies to lesions with low pro-

liferative potential and the possibility of cure following surgical resection alone.
- WHO grade II tumours are generally infiltrative in nature and, despite low-level proliferative activity, often recur and progress to higher grades of malignancy, e.g. low-grade diffuse astrocytomas can transform to anaplastic astrocytoma and glioblastoma. Similar transformation occurs over time in oligodendroglioma.
- WHO grade III is generally reserved for lesions with histological evidence of malignancy, including nuclear atypia and brisk mitotic activity. In most settings, patients with WHO grade III tumours receive adjuvant radiation and/or chemotherapy.
- WHO grade IV is assigned to cytologically malignant, mitotically active, necrosis-prone tumours typically associated with rapid pre- and post-operative disease evolution and a fatal outcome. Widespread infiltration of surrounding tissue and a propensity for cranio-spinal dissemination characterise some WHO grade IV malignancies, such as medulloblastoma, but is rare in others, including glioblastoma.

9.6.1.2. *Assessing CNS tumour transmission risk*

To date, the two most important factors in assessing CNS tumour transmission risk via organ transplant are:

1. the histologically determined WHO grade of a CNS tumour,
2. any interventions performed on the tumour (surgery, shunting, chemo- and radiotherapy).

A higher grade of tumour (WHO grade III or IV) and more interventions will lead to increased transmission risk. The specific tumour diagnosis adds important detail and will be used as supporting information.

9.6.2. Registry data on central nervous system tumours

Several clinical cases of transmission of CNS malignancies through organ transplantation have been reported in the literature [5, 27, 32, 202-216]. Most of the reported cases are related to high-grade CNS tumours, usually in association with other risk factors for extracranial metastases, and hence for transmission from donor to recipient. However, cases of transmission have been reported in which no other risk factors, except for the high grade of the tumour, were involved [217].

Follow-up registries containing information on organs transplanted from donors with a CNS malignancy have shown a low risk of disease transmission, placing the above-mentioned cases in perspective. In 1999 the Australian and New Zealand Organ Donation Registry published details of a series of 46 donors with a primary CNS tumour, of which 28 tumours were classified as malignant including four gliomas, four glioblastomas, 10 astrocytomas, five medulloblastomas, one high-grade meningioma and four histologically unspecified tumours. Seven donors had undergone a craniotomy, of whom three had ventriculo-peritoneal shunts; three others had ventriculo-peritoneal shunts without craniotomy. None of the 96 recipients of organs from these donors developed a transmitted tumour [218].

The Czech Republic has reported no cases of transmission among 89 patients receiving organs (79 kidneys, five livers, four hearts and one lung) from 41 donors with CNS malignancies (13 meningiomas, nine glioblastomas, three astrocytomas, two medulloblastomas, one craniopharyngioma, one acoustic neuroma, two pituitary adenomas, one lymphoma and eight histologically unspecified tumours) [219].

Similarly, in 2002, the UNOS registry published details of a series of 397 donors with a history of a primary CNS tumour who donated organs to 1 220 recipients, including 574 kidneys, 293 livers, 192 hearts, 76 lungs, 60 kidney-pancreas, 16 pancreas, six heart-lungs and three intestinal transplants [28]. CNS tumour type was not routinely reported to the UNOS registry before 1999, so the histological type of most tumours was not known. However, two donors were reported to have a medulloblastoma and 17 had a glioblastoma. These 19 donors with known high-grade tumours supplied a total of 56 transplanted organs: 26 kidneys, two kidney-pancreas, 15 livers, 10 hearts and three lungs. After an average follow-up of 36 months, no tumour transmission had been detected among the recipients.

In a later publication, based on a review of donors from the years 2000 to 2005 with a previous history of malignancy (as reported to the UNOS registry), 642 recipients had received transplanted organs from donors with a previous history of CNS malignancy, including 175 transplants from donors with a history of glioblastoma [26]. Three recipients (kidney, liver, lung) died following the transmission of a glioblastoma from the same donor, a donor noted to have an enlarged hilar lymph node at organ retrieval which was later shown to contain metastatic glioblastoma [26, 27].

In line with the low rate of transmission reported from the above-mentioned registries, a series

of 448 recipients (495 organs) transplanted between 1985 and 2001 with organs from 177 donors with CNS tumours was reviewed in the UK [36]. The types of CNS tumour included (according to the 2007 WHO classification) astrocytoma (astrocytoma unspecified, pilocytic, gemistocytic, fibrillary), gliomatosis cerebri, glioblastoma, giant cell glioblastoma, oligodendroglioma, ependymoma, malignant glioma not otherwise specified, mixed malignant glioma meningioma, medulloblastoma, Ewing's sarcoma, primitive neuro-ectodermal tumour, pineoblastoma, malignant neoplasm (without any specific, identified morphology), dermoid cyst with malignant transformation and haemangioblastoma. There was a wide range in the time-span of tumour diagnoses in donors prior to their deaths: 119 donors were diagnosed in the last 30 days before death, 23 donors between 31 days and 1 year before death, 16 between 1 and 3 years before, and 19 over 3 years prior to their death. Organs transplanted from these donors included 279 kidneys, one double kidney, 72 livers, one combined liver-kidney, 12 heart-lungs, 13 double lungs, 51 hearts, 10 single lungs, eight combined pancreas-kidney and one isolated pancreas. None of the 448 recipients developed a donor-transmitted malignancy within the minimum follow-up of 5 years.

Based on this experience and a review of the available literature, SaBTO in the UK estimated the risk of extraneural spread of all histological types of CNS malignancies (metastases and lymphoma excluded) as being 1.5 % (upper-95 % confidence interval limit). For WHO grade IV tumours the risk was estimated as 2.2 %, with a 6.4 % upper-95 % confidence limit [11, 220]. The risk of extraneural metastases related to the presence of ventricular shunts was estimated to be an additional 1 %, and doubts were raised about the risk related to prior surgery, chemotherapy and/or radiotherapy. This committee recommended providing these estimates when advising recipients undergoing transplantation with organs from donors with CNS malignancies, along with information on the survival benefits compared to remaining on the waiting list.

The most recent registry report is from South Korea, in which 91 recipients of organs from 28 donors with CNS tumours are described. These included three grade IV tumours (one each of medullobastoma, glioblastoma and mixed germ cell tumour), three grade III tumours (two astrocytomas, one pineal parenchymal tumour of intermediate differentiation) and 11 grade II tumours. There was no transmission reported.

The registry reports above need to be considered with a degree of circumspection since it is likely that most donors with high-grade tumours from whom organs had been used would not have had ventriculo-peritoneal or ventriculo-atrial shunts, and might not have had extensive resections. Data on the treatment of the donors prior to donation are lacking in most registry and case reports.

In contrast to those studies reporting a low transmission risk, the IPITTR published data suggesting that the risk of transmission of primary CNS tumours is high [33]. The IPITTR assessed a number of risk factors for transmission of primary CNS malignancies: high-grade tumour, presence of ventriculo-peritoneal or ventriculo-atrial shunts, prior craniotomy, systemic chemotherapy and radiation therapy. The registry received voluntary reports of 62 recipients who were transplanted between 1970 and 2002 with organs from 36 donors diagnosed with primary CNS malignancy (16 astrocytomas, 15 gliomas or glioblastomas, three medulloblastomas and two cerebellar tumours). Of the 36 donors, 24 received some form of cancer therapy before organ donation, including ventriculoperitoneal or ventriculo-atrial shunts (12), craniotomy (six), radiation therapy (four) and chemotherapy (two), and 62 organs were transplanted from the 36 donors, including 35 kidneys, 12 hearts, 10 livers, two pancreas and three lungs.

Based on the data in its registry, the IPITTR estimated a 7 % transmission rate of CNS tumours in the absence of the aforementioned risk factors, 36 % if at least one was present, and 43 % if two were present. A high-grade (WHO III or IV) malignancy alone was associated with a 43 % transmission rate. The high estimated risk of CNS malignancy transmission described by the IPITTR, in contrast with other registries, has to be interpreted with caution. Since cases of cancer in recipients are reported to the IPITTR on a voluntary basis, it is subject to reporting bias; cases of non-transmission may not be reported and the registry does not record the numbers of patients at risk from which the reported cases occur [221].

In 2011, based on information available at the time of their report, the DTAC Malignancy Subcommittee in the USA assigned WHO III-IV CNS tumours to the high-risk category of transmission (> 10 %), along with any CNS tumour (regardless of grade) that had other risk factors for disease transmission [8]. However, the DTAC Malignancy Subcommittee noted that some WHO grade IV tumours might present only an intermediate risk of transmission and that this issue needed to be addressed in a comprehensive, evidence-based fashion. Their quantitative approach to risk estimates suggested that future revisions may take more recent data

into account and in some cases revise risk estimates downward. Corresponding data have been published by SaBTO [11], where WHO grade IV tumours have been categorised in the intermediate risk group according to the national data.

9.6.3. Classification of risk for central nervous system tumours

Drawing on the available information and the variable estimates of disease transmission derived from the previously described registries, there is a widely accepted qualitative classification of CNS ma-

Table 9.4. **Grading of selected central nervous system tumours (WHO 2016 classification)**

Diffuse astrocytic and oligodendroglial tumours	**I**	**II**	**III**	**IV**
Diffuse astrocytoma, IDH-mutant		•		
Anaplastic astrocytoma, IDH-mutant			•	
Glioblastoma, IDH-wildtype				•
Glioblastoma, IDH-mutant				•
Diffuse midline glioma, H3K27 M-mutant				•
Oligodendroglioma, IDH-mutant and 1p/19q-codeleted		•		
Anaplastic oligodendroglioma, IDH-mutant and 1p/19q-codeleted			•	
Other astrocytic tumours	**I**	**II**	**III**	**IV**
Pilocytic astrocytoma	•			
Subependymal giant cell astrocytoma	•			
Pleomorphic xanthoastrocytoma		•		
Anaplastic pleomorphic xanthoastrocytoma			•	
Ependymal tumours	**I**	**II**	**III**	**IV**
Subependymoma	•			
Myxopapillary ependymoma	•			
Ependymoma		•		
Ependymoma, *RELA* fusion-positive		•	•	
Anaplastic ependymoma			•	
Other gliomas	**I**	**II**	**III**	**IV**
Angiocentric glioma	•			
Chordoid glioma of third ventricle		•		
Choroid plexus tumours	**I**	**II**	**III**	**IV**
Choroid plexus papilloma	•			
Atypical choroid plexus papilloma		•		
Choroid plexus carcinoma			•	
Pineal tumours	**I**	**II**	**III**	**IV**
Pineocytoma	•			
Pineal parenchymal tumour of intermediate differentiation		•	•	
Pineoblastoma				•
Papillary tumour of the pineal region		•	•	
Meningiomas	**I**	**II**	**III**	**IV**
Meningioma	•			
Atypical meningioma		•		
Anaplastic (malignant) meningioma			•	

Embryonal tumours	**I**	**II**	**III**	**IV**
Medulloblastoma (all subtypes)				•
Embryonal tumour with multi-layered rosettes, C19MC-altered				•
Medulloepithelioma				•
CNS embryonal tumour, not otherwise specified				•
Atypical teratoid/rhabdoid tumour				•
CNS embryonal tumour with rhabdoid features				•
Neuronal and mixed neuronal-glial tumours	**I**	**II**	**III**	**IV**
Dysembryoplastic neuroepithelial tumour	•			
Gangliocytoma	•			
Ganglioglioma	•			
Anaplastic ganglioglioma			•	
Dysplastic gangliocytoma of cerebellum (Lhermitte–Duclos)	•			
Desmoplastic infantile astrocytoma and ganglioglioma	•			
Papillary glioneuronal tumour	•			
Rosette-forming glioneuronal tumour	•			
Central neurocytoma		•		
Extraventricular neurocytoma		•		
Cerebellar liponeurocytoma		•		
Tumours of the cranial and paraspinal nerves	**I**	**II**	**III**	**IV**
Schwannoma	•			
Neurofibroma	•			
Perineurioma	•			
Malignant peripheral nerve sheath tumour (MPNST)		•	•	•
Mesenchymal, non-meningothelial tumours	**I**	**II**	**III**	**IV**
Solitary fibrous tumour/haemangiopericytoma	•	•	•	
Haemangioblastoma	•			
Tumours of the sellar region	**I**	**II**	**III**	**IV**
Craniopharyngioma	•			
Granular cell tumour	•			
Pituicytoma	•			
Spindle cell oncocytoma	•			

Source: adapted from: [184]. Louis DN, Perry A, Reifenberger G *et al*. The 2016 WHO Classification of Tumors of the Central Nervous System: a summary. *Acta Neuropathologica* 2016;131(6):803-20.

lignancies, based on the risk of tumour transmission, as shown below.

- WHO grade I and II tumours – minimal risk of tumour transmission.
- WHO grade III tumours – previous classifications have categorised these malignancies as high-risk. Recent analyses indicate that this may overestimate the risk, and SaBTO/UK assesses them as a low risk for tumour transmission. Until this is supported by larger evidence in the literature, these malignancies should be accepted as low to intermediate risk if no risk factors are present (resection, ventriculo-peritoneal or ventriculo-atrial shunt, chemo-/radiotherapy). The risk is increased to high risk in the presence of any risk factors.
- WHO grade IV tumours – former classifications have categorised these tumours as an unacceptable risk. Recent analyses indicate that this may overestimate the risk, since several transplants without transmission have been reported. SaBTO/UK assesses them as an intermediate risk of tumour transmission. Until this is supported by larger evidence in the literature, these malignancies should only be accepted with some caution on a case-by-case basis as intermediate to high risk. The risk is increased particularly in the presence of ventriculo-peritoneal or ventriculo-atrial shunts, as well as previous resection or chemo-/radiotherapy.
- Primary cerebral lymphoma – unacceptable risk of tumour transmission.

Beyond WHO grading, the risk factors outlined above should be taken as additional elements for assessing the risk of extracranial spread of a primary malignant cerebral tumour. This assessment should include exact documentation of all interventions (resection/shunting, chemo- and radiotherapy). At organ procurement, it is recommended that a thorough laparotomy and thoracotomy is performed, as well as inspection of cervical lymph nodes, the scalp over any resection site, and any shunt that may be present to exclude extracranial growth.

9.7. Review of specific tumours of the central nervous system

9.7.1. Neuro-ectodermal tumours

9.7.1.1. *Medulloblastoma*

Medulloblastoma (WHO grade IV) is the most common primitive neuro-ectodermal tumour and represents 6 % of all intracranial gliomas and 44 % of gliomas in children. Normally, these tumours originate in the fourth ventricle, cerebellar vermis or hemispheres, and often cause hydrocephalus requiring shunts. Medulloblastomas that occur during childhood are the ones that most frequently metastasise outside the cerebrospinal axis. Extraneural metastases have been observed in 7 % of cases and some authors suggest that this prevalence could be even higher. In one old series of 77 children with medulloblastomas, eight (10 %) developed metastases; there was no significant difference in incidence whether they had previously had a ventriculo-peritoneal shunt (3 of 40) or not (5 of 37) [222]. All patients with metastatic disease had undergone complete or subtotal resection and cranial irradiation.

In another series, 1 % of 1 011 patients with CNS tumours developed extraneural metastases, of which six were children with medulloblastomas [223]. In a third series, 3.6 % of children with medulloblastoma developed extraneural metastases [224]. A more recent series reports 14 (4.8 %) of 292 patients with medulloblastoma who developed extracranial metastases [225]. All four series report bone, bone marrow and cervical lymphatic glands as common sites for metastatic medulloblastoma, with intra-abdominal and intra-thoracic metastases less common.

Cancer transmission from organ donors with medulloblastomas to recipients has been described. Lefrançois *et al.* [202] documented tumour transmission from a donor with a medulloblastoma to three recipients (heart, renal and kidney-pancreas) 5 months after the transplant. The donor had a ventriculo-atrial shunt and had undergone surgery, radiotherapy and chemotherapy. The IPITTR has registered seven organ recipients from three donors with medulloblastomas, all with a prior ventriculo-peritoneal shunt [33]. Three of the seven recipients presented with tumour transmission within 5-7 months of the transplant. Of these three recipients, two died of metastatic disease and the third had diffuse metastatic disease at the time of reporting. Based on this experience, the IPITTR contraindicates the use of organs from donors with these types of malignancy because of the high risk of transmission to recipients. Currently, patients with medulloblastoma are accepted as organ donors in exceptional cases. Valid data for a reasonable risk estimation are pending.

So-called neuro-ectodermal tumours should be considered like medulloblastomas.

Assessing risk from medulloblastomas in transplants

Childhood medulloblastomas are the CNS primitive tumours that metastasise most frequently outside

the CNS. The risk may be increased if prior ventriculo-peritoneal or ventricular-atrial shunts, tumour resection or cranial chemo-/radiotherapy have been performed.
Organs from potential donors with medulloblastomas (WHO grade IV) are considered intermediate to high risk for tumour transmission, depending on different international recommendations, which will be adjusted with increasing evidence. They should be used exclusively for transplants where the recipient's risk of dying while on the waiting list is greater than the risk of tumour transmission.

9.7.1.2. *Gliomas*

Gliomas comprise astrocytomas, oligodendrogliomas and ependymomas. The incidence of extracranial glioma dissemination is calculated to be 0.4-2.3 %, mostly from glioblastoma and predominantly to the lung, pleura, lymph nodes, bone and liver [197]. One confounding factor in interpreting published data on the behaviour of gliomas is the security of the histological diagnosis. In one large national study where histology was reviewed, only 59 % of 258 patients believed to have an ependymoma were confirmed to have one, with other tumours ranging from meningiomas (n = 2) to glioblastomas (n = 34, 13 %) being misdiagnosed [226].

9.7.1.2.1. Astrocytomas

Astrocytomas are divided into:

a. low-grade astrocytomas: pilocytic astrocytoma (WHO grade I) and diffuse astrocytoma (WHO grade II) represent 20 % and 55 % of all low-grade intracranial gliomas respectively;
b. malignant astrocytomas: anaplastic astrocytoma (WHO grade III) and glioblastoma (WHO grade IV); glioblastoma being the most common intracranial glioma.

Pilocytic astrocytoma (WHO grade I) and low-grade astrocytomas (WHO grade II)

Low-grade astrocytomas are normally found in children and young adults. They rarely metastasise through the cerebrospinal axis, although they may invade the leptomeninges. Metastases occur with greater frequency if tumour growth reaches the ventricular ependyma or if there is progression to anaplastic (malignant) glioma. Pollack *et al.* [227] described one of 76 patients with low-grade astrocytomas who developed peritoneal metastases and ascites two months after tumour resection and placement of a ventriculo-peritoneal shunt. Arulrajah *et al.* [228] described a child with a pilomyxoid astrocytoma of the cervical cord with leptomeningeal metastases who developed peritoneal metastases 2 years after resection and placement of a ventriculo-peritoneal shunt. Schroder *et al.* [229] described a female who had had a pilocytic astrocytoma of the spinal cord treated in infancy with surgery and radiotherapy, which presented 26 years later as metastases.

Up to 30 % of low-grade astrocytomas may be associated with more aggressive histological grades. These tumours have a tendency to relapse and frequently present as a higher grade of tumour.

Assessing risk from astrocytomas in transplants

Potential donors with pilocytic astrocytoma (WHO grade I) may be considered for organ donation with minimal risk of transmission.
Extraneural metastases from low-grade astrocytomas (WHO grade II) are rare, and have been associated with resection and ventriculo-peritoneal shunts. In the absence of these risk factors, the donor may be considered minimal-risk. Risk may increase with the extent of performed interventions.
A complete histological examination of the tumour should be performed so that areas of transformation into a more aggressive malignancy can be ruled out.
Since astrocytomas have a tendency to relapse with a histologically higher grade of malignancy, new histological examinations to regrade the tumour should be performed where relapse occurs.
If the tumour co-exists with histological areas of greater malignancy or is very invasive locally, it should be considered high-grade and will be associated with an increased risk of transmission.

Anaplastic astrocytomas (WHO grade III) and glioblastoma (WHO grade IV)

At least 80 % of malignant gliomas are glioblastoma, representing the most biologically aggressive type of primary CNS tumour in adults. They can be located in any part of the brain, but normally affect the cerebral hemispheres. Anaplastic astrocytomas appear more frequently in adults aged in their thirties and forties, while glioblastoma more often presents in adults aged in their fifties and sixties. Although direct dissemination rarely occurs through the *dura mater* without prior surgical intervention, transgression of the *dura mater* can occur with greater ease when ventriculo-peritoneal shunts or radiotherapy have been performed.

Dissemination of a glioblastoma through the cerebrospinal fluid is not uncommon, and generally occurs because of invasion or rupture within the ventricular cavity. Extracranial metastases of anaplastic astrocytomas and glioblastoma have been observed in the absence of prior surgery [198, 206], although they occur with greater frequency following surgery or ventriculo-peritoneal drainage [230]. When extraneural metastases do occur from anaplastic astrocytomas and glioblastomas, they are most commonly

found in bone (especially vertebrae), liver, lungs and cervical lymph nodes [231].

Transmission of cancer from donors with glioblastoma has been documented in individual reports [5, 26, 27, 204-206, 208, 209]. The reported cases usually occurred where donors had undergone prior surgery and/or received some form of cancer therapy. Recipients affected were kidney, liver and lung transplant patients. Glioblastoma transmission to heart recipients has not been reported [32, 232].

Fecteau *et al.* [233] described the case of a patient with peritoneal metastases 9 months after a ventriculo-peritoneal shunt, which was discovered during an organ-procurement procedure and prevented transplantation from taking place.

The IPITTR has described a series of 25 organ transplants from 16 donors with astrocytomas, during the period 1970-2002, in which 14 of those organs had risk factors for tumour transmission: four WHO grade III/IV astrocytomas, five prior craniotomies, four prior radiotherapy and four prior chemotherapy [33]. There was one case of tumour transmission 20 months after transplantation, in which the donor presented a single risk factor (astrocytoma WHO grade III/IV). Of 26 organ transplants from 15 donors with gliomas or glioblastomas, eight were associated with high WHO grade III/IV glioblastomas and 18 with other gliomas. Of these, 15 had some risk factors (10 prior craniotomies and nine had high WHO grade III/IV gliomas), and eight tumour transmissions occurred 2-15 months after transplantation. It has been suggested that 70 % of glioblastomas exhibit elevated levels of certain growth factors (Akt and mTOR). This would favour the development of extraneural metastases and suggests the possible utility of mTOR inhibitors as immunosuppressant drugs for organ recipients in such donor cases [209].

Gliosarcoma, a subtype of glioblastoma, has also been described to cause extracranial metastases [234].

Assessing risk from anaplastic astrocytomas and glioblastomas in transplants

Spontaneous extraneural metastases of anaplastic astrocytomas and glioblastoma are rare, but such metastases have been observed, and seem to occur more frequently when associated with prior surgical treatment and/or ventriculo-peritoneal drainage, or chemo-/radiotherapy.
Potential donors with anaplastic astrocytomas (WHO grade III) can be accepted as organ donors.
Transmission risk is considered low to intermediate for tumours without any risk factors.
Potential donors with glioblastoma (WHO grade IV) are considered intermediate to high risk for transmission, depending on different national recommendations, which are expected to be adjusted with increasing evidence.
The transmission risk is increased (high risk) in all cases with previous interventions such as tumour resection, ventriculo-peritoneal/-atrial drainage and/or cranial chemo-/radiotherapy.

9.7.1.2.2. Oligodendrogliomas

Oligodendrogliomas represent 5 % of primary brain tumours [235]. There are two main types: low-grade oligodendrogliomas (WHO grade II) and anaplastic oligodendrogliomas (WHO grade III). Recent advances in molecular genetics, incorporated into the WHO-2016 revised classification of CNS tumours, have made the diagnosis of oligodendroglioma dependent on the demonstration of IDH mutations and co-deletion of chromosomes 1p and 19q. They are more sensitive to chemotherapy than the equivalent grade of astrocytoma [236].

Low-grade oligodendrogliomas (WHO grade II) are the most frequent form. They typically appear in adults aged in their twenties and thirties. They grow slowly, diffusely infiltrate the white matter, cortex and even the leptomeninges, and often progress over time to become anaplastic oligodendrogliomas (WHO grade III). They are extensively vascularised and may occasionally present as spontaneous cerebral haemorrhage.

Anaplastic oligodendrogliomas are very aggressive tumours that behave like glioblastoma. Extracranial metastases of anaplastic oligodendrogliomas have been observed after multiple craniotomies [237], with typical sites being scalp, lymph nodes, bone and bone marrow [238]. To date, no cases of oligodendroglioma transmission to organ recipients have been published.

Assessing risk from oligodendrogliomas in transplants

Low-grade oligodendrogliomas (WHO grade II) represent a minimal risk of tumour transmission.
Anaplastic oligodendrogliomas (WHO grade III) without any risk factors are considered low to intermediate risk.
Donors with anaplastic oligodendrogliomas (WHO grade III) who have previously undergone interventions such as tumour resection, ventriculo-peritoneal/-atrial drainage and/or cranial chemo-/radiotherapy, are associated with an increased risk (high risk) of tumour transmission.

9.7.1.2.3. Mixed gliomas

These gliomas are WHO grade II/III and have the characteristics of oligodendrogliomas and astrocytomas [209]. Genotypic analysis (IDH mutation

and 1p/19q co-deletion status) combined with phenotype should in future be able to assign such tumours as either oligodendrogliomas or astrocytomas.

Assessing risk from mixed gliomas in transplants

The transmission risk of mixed gliomas is equivalent to other gliomas and is classified according to the WHO grade of the tumour (see above, quick reference box in §9.6.3).

9.7.1.2.4. Ependymomas

Ependymomas derive from the ependymal cells that line the ventricles and central canal of the spinal cord. They represent 6 % of all intracranial gliomas and are the third most common brain tumour in children. In fact, 50-70 % of ependymomas are infratentorial, are located in the IVth ventricle, and manifest in the first two decades of life. Supratentorial ependymomas can appear at any age and grow in the ventricular cavities or invade the nervous system parenchyma, especially in the parieto-occipital region. They rarely metastasise outside the CNS, although extraneural metastases of the intracranial and spinal ependymoma have been observed, but the majority were recurrent neoplasms in which the extraneural dissemination followed tumour invasion of the adjacent soft tissues or resulted from seeding at surgery [239-241].

In a series of 81 ependymomas, Newton *et al.* [242] reported five cases (6.2 %) with extracranial dissemination. Two of these tumours were histologically anaplastic and three were benign. Three of the patients had undergone previous resection and one a biopsy but, in the fifth patient, extraneural metastases were present at initial diagnosis. There was no correlation between development of extraneural metastases and prior radiotherapy or chemotherapy. Tumours metastasised into the lungs, thoracic lymphatic nodes, pleura, peritoneum and liver. Both patients with peritoneal metastases had had ventriculo-peritoneal shunts. Extraneural metastases did not correlate with histologic grade or degree of surgical resection. Another case of extracranial spread (bone metastases) of an anaplastic ependymoma present at initial tumour diagnosis has been described [243], but most reports have followed multiple surgical resections, radiotherapy and chemotherapy [244-248].

To date, no case of transmission of ependymomas to an organ recipient has been reported.

Assessing risk from ependymomas in transplants

Extraneural ependymoma metastases occur, and the cases observed correspond to recurrent neoplasms or those treated with radiotherapy and/or chemotherapy.

The transmission risk of organs from donors with ependymomas is considered to depend upon the histological WHO grade of the tumour, so a low-grade (WHO grade I or II) ependymoma represents minimal risk of transmission, whereas an anaplastic ependymoma (WHO III) will be associated with low to intermediate risk.
The transmission risk is increased (high risk) in cases with previous interventions such as tumour resection, ventriculo-peritoneal/-atrial drainage and/or cranial chemo-/radiotherapy.

9.7.1.3. *Choroid plexus tumours*

Choroid plexus tumours represent less than 1 % of all neuro-epithelial tumours [235]. They are more often supratentorial in children, but in adults they are more frequent in the IVth ventricle and in the cerebello-pontine angle. Those located in the cerebello-pontine angle are more often benign.

Choroid plexus papillomas are the most frequent tumours and are histologically benign.

Choroid plexus carcinomas are aggressive, malignant tumours (WHO grade III) that can metastasise outside the CNS [249].

To date, no cases of transmission of choroid plexus tumours to organ recipients have been reported, but that may reflect the rarity of the tumour.

Assessing risk from choroid plexus tumours in transplants

Organs from potential donors with choroid plexus papillomas may be considered minimal risk for transmission.
Organs from potential donors with choroid plexus carcinomas (WHO grade III) without any risk factors are considered low to intermediate risk.
The transmission risk of choroid carcinomas is increased (high risk) in cases with previous interventions such as tumour resection, ventriculo-peritoneal/-atrial drainage and/or cranial chemo-/radiotherapy.

9.7.1.4. *Pineocytomas and pineoblastomas*

Parenchymal tumours of the pineal gland are rare; they include pineocytomas (WHO grade I), pineoblastomas (WHO grade IV) and pineal parenchymal tumours of indeterminate differentiation (WHO grade II or III). Little is known about the behaviour of pineocytomas since some remain well-delimited without exhibiting any aggressive behaviour, while others metastasise through the cerebrospinal fluid and behave like pineoblastomas.

Pineoblastomas are rare tumours that correspond to a more primitive form of pineocytoma. These tumours are highly malignant and, biologically, they behave similarly to medulloblastomas, showing

a clear tendency to disseminate in the cerebral-spinal cord. Extraneural metastases have been reported, including bone metastases and tumour spread in association with a ventriculo-peritoneal shunt [250] [251-253].

There has been a single report of transmission of a pineoblastoma to a multivisceral transplant recipient. The donor was a 14-month-old infant who presented in a coma with severe brain injury and was thought to be a victim of shaking; autopsy demonstrated a pineal tumour with meningeal spread, but no other visible spread [210].

Assessing the risk from pineocytomas and pineoblastomas in transplants

Organs from potential donors with pineocytomas (WHO grade I) may be considered minimal risk for transmission.
Organs from potential donors with pineoblastomas (WHO grade IV) are considered intermediate to high risk, depending on the different international recommendations, which will be adjusted with increasing evidence.
Parenchymal tumours of indeterminate differentiation (WHO grade II or III) without any risk factors should be accepted according to WHO grade III if differentiation cannot definitely be assigned.
The transmission risk is increased (high risk) in cases with previous interventions such as tumour resection, ventriculo-peritoneal/-atrial drainage and/or cranial chemo-/radiotherapy.

9.7.2. Other intracranial tumours

9.7.2.1. *Benign meningiomas, atypical meningiomas, anaplastic (or malignant) meningiomas*

Meningiomas represent 20 % of all intracranial tumours and can manifest at any age. Typically they occur in adults, and more frequently in women. Fewer than 10 % of them are multiple meningiomas, which can appear sporadically or be associated with type 2 neurofibromatosis.

Meningiomas are usually benign. Although invasion of the adjacent tissues is frequent, dissemination outside the affected organ is less so. Nevertheless they can occasionally behave in an invasive manner with a significantly worse prognosis. Approximately 5 % of meningiomas are atypical and 2 % are malignant.

Anaplastic or malignant meningiomas are aggressive meningeal tumours that are frequently associated with multiple recurrences and extracranial metastases. Younis *et al.* [254] presented a series of 18 patients with aggressive meningeal tumours, of which 12 were malignant (anaplastic) meningiomas (WHO III) and six atypical meningiomas (WHO II). Three (16 %) developed extracranial metastases (two malignant meningiomas and one atypical meningioma). In these three cases, pulmonary and bone metastases were the most frequent. All three patients had undergone total surgical excision, radiotherapy and chemotherapy, and metastases developed 26, 96 and 108 months after initial diagnosis. Other authors have reported cases of extraneural metastases, with local scalp recurrence, as well as metastases to lung, liver and bone [255-262]. One study suggested that meningiomas expressing high levels of CD90 were atypical and more likely to metastasise [259].

The transmission of a malignant meningioma (originally diagnosed as a grade II astrocytoma) through a kidney transplant with peritoneal invasion and liver metastases was described by Bosmans *et al.* [207]. The tumour regressed following transplant nephrectomy and interferon alpha treatment.

Assessing the risk from meningiomas in transplants

Extraneural metastases by histologically benign meningiomas are very rare. Organs from potential donors with these types of tumour have a minimal risk of transmission.
Anaplastic or malignant meningiomas (WHO grade III) are more aggressive meningeal tumours that can occasionally be associated with extraneural metastases. Organs from potential donors with these tumours are considered low to intermediate risk if no risk factors are present.
The transmission risk of anaplastic or malignant meningiomas is increased (high risk) in cases with previous interventions such as tumour resection, ventriculo-peritoneal/-atrial drainage and/or cranial chemo-/radiotherapy.

9.7.2.2. *Malignant mesenchymal tumours: anaplastic haemangiopericytomas*

Anaplastic haemangiopericytomas (WHO III) are locally aggressive meningeal tumours that are frequently associated with multiple recurrences and extraneural metastases [263]. Younis *et al.* [254] described four cases of haemangiopericytoma and three meningeal sarcomas (now reclassified as either anaplastic haemangiopericytoma or anaplastic meningioma) in a review of aggressive meningeal tumours. Three of these seven cases developed extracranial metastases; two haemangiopericytomas metastasised within 96 and 102 months while the meningeal sarcoma had metastasised in multiple organs within 3 months of the initial diagnosis. Kaneko *et al.* [264] reviewed 20 cases of haemangiopericytoma with extraneural metastases, commonly to bone, liver, lung and lymph nodes. Late pancreatic and bone occur-

rence of extracranial metastases, 22 years after apparently curative craniectomy, has also been described [265]. Note that even non-anaplastic haemangiopericytoma (WHO II) is prone to haematogenous metastases.

No cases of transmission of meningeal/ anaplastic haemangiopericytoma from organ donor to recipient have been reported in the literature so far, but this should not give a false sense of security.

Assessing the risk from anaplastic haemangiopericytomas in transplants

Organs from potential donors with anaplastic haemangiopericytomas (WHO grade III) are considered intermediate to high risk for tumour transmission, depending on the different international recommendations, which will be adjusted with increasing evidence.
Organs from potential donors with haemangiopericytomas (WHO grade II) without any risk factors represent a minimal to intermediate risk for tumour transmission.
The transmission risk for donors with any kind of haemangiopericytoma is further increased in cases with previous interventions such as tumour resection, ventriculo-peritoneal/-atrial drainage and/or cranial chemo-/radiotherapy.

9.7.2.3. *Haemangioblastomas*

Haemangioblastomas are benign tumours of the blood vessels that occur with greatest frequency in the cerebellum. Dissemination of haemangioblastoma is rare, although Hoffman *et al.* [266] observed two spontaneous cases of extraneural metastases.

In 20 % of cases, haemangioblastomas appear to be associated with other tumours as part of Von Hippel–Lindau syndrome, which is also associated with a high incidence of RCC.

Assessing the risk from haemangioblastomas in transplants

Due to the usually benign behaviour of haemangioblastomas, organs from potential donors with this diagnosis may be considered minimal risk for tumour transmission, provided that coincidental neoplasms and the existence of Von Hippel–Lindau syndrome are ruled out.
Any recommendation for a particular tumour must be considered in the context of any coincidental neoplasms. In the case of Von Hippel–Lindau syndrome, particular attention must be paid to possible coincidental neoplasms.

9.7.2.4. *Germ-cell tumours*

Intracranial germ-cell tumours most frequently arise in the pineal gland, and approximately half of all pineal tumours are germ-cell tumours. These include germinoma, embryonal carcinoma, yolk sac tumour, choriocarcinoma, mature and immature teratoma, and teratocarcinoma; many are of mixed cell type with different elements of germ cell tumour. They are histologically malignant, infiltrating tumours that usually disseminate through the third ventricle. Non-germinomatous germ-cell tumours may be associated with increased levels of human choriogonadotropin (HCG), alpha-fetoprotein (AFP) and placental alkaline phosphatase in serum and cerebrospinal fluid. Extra-gland metastases have been observed following craniotomies, cranial-spinal radiotherapy or ventriculo-peritoneal shunts [266].

Extragonadal choriocarcinoma is a type of teratoma that occurs in the pineal region. They are highly malignant tumours with a tendency to invade adjacent structures. Extracranial metastases have been reported in the lungs [267].

Assessing the risk from germ-cell tumours in transplants

Organs from potential donors with mature teratomas represent a minimal risk of tumour transmission.
Organs from donors with other germ-cell tumours should be considered intermediate to high risk for tumour transmission, depending on the different international recommendations, which will be adjusted with increasing evidence.
The transmission risk is further increased in cases with previous interventions, such as tumour resection, ventriculo-peritoneal/-atrial drainage and/or cranial chemo-/radiotherapy.

9.7.2.5. *Chordomas*

Chordomas arise from remnants of the embryonic notochord and are slow-growing, locally invasive tumours that can lead to extracranial metastases [268].

Assessing the risk from chordomas in transplants

Organs from potential donors with chordomas should probably be considered high-risk for tumour transmission, but there are no recommendations available in the current literature.

9.7.2.6. *Primary cerebral lymphomas*

Primary intracranial lymphomas appear with greater frequency in immunosuppressed patients, such as those diagnosed with AIDS. Their prognosis is bad and they progress to extracranial dissemination.

There is a reported transmission of a primary intracranial non-Hodgkin's lymphoma into both kidney recipients [17]. It was detected in the donor autopsy but not reported to the transplant centres because no distant metastases were found. Both re-

cipients underwent transplant nephrectomy and withdrawal of immunosuppression after the incidental diagnosis of transmitted lymphoma. One recipient had only localised graft disease and was free of recurrence after 10 months. The other recipient, who was found to have diffuse infiltration of the tissue surrounding the kidney, received radiotherapy and, due to lymphoblastic ascites, additional chemotherapy. He was in complete remission but died of pneumonia and pericarditis a few weeks later without signs of recurrent disease in autopsy.

A separate report documented transmission of an intracerebral anaplastic T-cell lymphoma from a donor suspected of having bacterial meningitis into four recipients, who received the liver, pancreas and kidneys [269]. The kidney and pancreas recipients survived following removal of the allografts and chemotherapy, but the liver recipient succumbed to tumour despite treatment.

Assessing the risk from primary cerebral lymphomas in transplants

Organs from donors with primary cerebral lymphomas have an unacceptable risk for tumour transmission and should not be considered for transplantation.

9.8. Recipient malignancy caused by donor oncogenic viruses

Some viruses that are either contracted from the donor or reactivated in the recipient as a consequence of immunosuppression can cause cancer in the transplant recipient. These are Epstein–Barr virus (EBV or HHV4), human herpes type 8 virus or Kaposi sarcoma virus (HHV8), hepatitis B virus (HBV), hepatitis C virus (HCV), human lymphotropic type 1 virus (human T-cell leukaemia virus, HTLV1), Merkel cell polyoma virus (MCPyV) and human papilloma virus (HPV) [270]. In populations without immunosuppression, especially in developing countries, 15-20 % of all cancers are related to infection with these oncogenic viruses [270, 271].

Intensified cancer surveillance is important in any organ recipient who may have acquired one of these oncogenic virus infections before and/or after transplantation. The likelihood of developing a cancer by contracting one of these viruses is unknown, but when it occurs it is often soon after transplantation in response to the higher immunosuppressive burden. The therapeutic options are often limited and/or preventive measurements should be considered, such as immunisation against the virus where vaccines are available (e.g. human papilloma virus if considering uterine transplantation).

Table 9.5 provides an overview of the currently known viruses with oncogenic potential and the implications for organ donation. The donor cancer screening protocol should identify such malignancies where they exist. In cases where such a malignancy is detected, please refer to the corresponding subsection of this chapter.

Note that exhaustive research into the issue of transmission risks associated with viral infection and cancer in the context of organ donation is still under way. Describing the detailed patho-mechanism of viral oncology is beyond the scope of this Guide. It is worthwhile to know that, in cancer, viral replication may be missing as this would lyse the host cell and prevent tumorigenesis. The virus may exist intracellularly as naked nucleic acid in the form of a plasmid or an episome, or as integrated into the genome. DNA-virus genome can integrate directly into the host genome whereas RNA-virus genome must undergo reverse transcription in advance. Specific intra- and intercellular signalling pathways are down- or upregulated for cancer growth. Currently undefined is the issue of co-infection viruses with oncogenic potential and other viruses interacting with up- and down-regulation of host defence mechanism, e.g. any combination of BK-virus, JK-virus, HPV, CMV, EBV, HSV etc. Some of these viruses infect people globally whereas for others regional or local different rates or subpopulations at risk are observed [272], which has implications for screening strategies and for strategies to reduce harm in recipients.

9.9. Donors with a genetic predisposition to cancer

Several genetic conditions predispose to cancer (Table 9.6). In a donor with a known genetic predisposition there are two considerations: first, careful examination of organs known to be at risk of developing malignancy, to ensure no active malignancy is present; second, transplanting an organ with a genetic risk of malignancy is unlikely to remove that genetic tendency, so is not advised. Where possible a local expert in cancer genetics should be consulted.

Table 9.5. **Viruses with known oncogenic potential**
Data are provided for a population without immunosuppression unless stated otherwise. (Clinical follow-up: targeted surveillance of recipient for development of such tumour. Type: H=haemotological, E=epithelial, M=mesenchymal)

Virus	Genome	Replication	Transmission	Cellular tropism	Primary infection	Screening of infection	Prevention	Population infected and regional prevalence	Malignancy	Type	Oncogenic viral particle; other mechanism	Recipient surveillance
HHV4 = EBV	double-stranded DNA, not integrated in host genome; IARC 1	lytic and latent stages; in cell nucleus via immediate mRNAs proteins encoded and DNA replicated	saliva; blood	B lymphocytes, epithelial cells	asymptomatic, infectious mononucleosis	serology	none	global >90 %	B-cell lymphoma	H	EBNA 1 (type 1 latency)	EBV monitoring, clinical follow-up
									Plasmablastic lymphoma	H		
									Burkitt lymphoma	H		
									Hodgkin lymphoma	H	EBNA C3, LMP1, LMP2 (type 2 latency)	
									T/NK-cell lymphoma	H	LMP1, LMP2 (type 2 latency)	
									Leukaemia/ Adult T-cell lymphoma	H		
									polymorphic post-transplant lympho-proliferative disorders (PTLD)	H	miR155 (type 3 latency)	
									Nasopharyngeal carcinoma	E	EBNA 1 (type 1 latency)	
									Gastric carcinoma	E		
									Lymphoepithelial carcinoma (e.g. stomach, oesophagus, salivary glands, tonsils, parotids, lung, intrahepatic bile duct)	E	EBNA 1, LMP1, LMP2 (type 1 & 2 latency)	
									Leiomyosarcoma	M	EBNA 1	
									Mesenchymal neoplasm	M		
									Follicular dendritic	M		

Virus	Genome	Replication	Transmission	Cellular tropism	Primary infection	Screening of infection	Prevention	Population infected and regional prevalence	Malignancy	Type	Oncogenic viral particle; other mechanism	Recipient surveillance
HHV8 = KSHV	double-stranded DNA, not integrated in host genome; IARC 1	lytic and latent stages; in cell nucleus via immediate mRNAs proteins encoded and DNA replicated	sexual (MSM), else poorly defined	B lymphocytes, peripheral mononuclear cells (BPMC)	asymptomatic	reliable test currently not available	none	global 10 %; Mediterranean, sub-Saharan Africa, northwest China	Non-Hodgkin lymphoma	H	vCyC	identify at risk (serology?), clinical follow-up
									Kaposi sarcoma	M	LANA 1, Prox 1, vFlip, kaposins A, B, C & ORF K1, miR-K12-1, miR-K12-3, miR-K-12-7	
HBV	circular double-stranded DNA, integrated in host genome (e.g. ccDNA); IARC 1	in cell nucleus viral DNA & RNA polymerases produce virus, reverse transcriptase encodes viral DNA	sexual, parenteral, vertical, any blood contact	hepatocyte	acute hepatitis or chronic infection (10 %)	serology, NAT	vaccination, treatment by antivirals if chronic virus replication, 'hygiene'	global 5 %; sub-Saharan Africa, Southeast Asia, Inuit	HCC	E	pre-S2, delete mutation proteins, STAT & NF-KB, viral protein HBx// inflammatory environment, oxidative stress, dysregulated control of microRNAs, virus products	HBV NAT, HBV treatment, clinical follow-up
HCV	RNA, not integrated in host genome; IARC 1	in cytoplasm: denudation > translation in polyprotein > fragmented polymerase for transcription and replication	sexual, parenteral, (vertical), any blood contact	hepatocyte, B lymphocyte, dendritic cells	acute hepatitis or chronic infection (5 %), asymptomatic	serology, NAT	10-25 % spontaneous clearance, else: Direct Acting Antivirals (DAAs), 'hygiene'	global 3 %, North Africa, Southeast Asia, eastern Mediterranean, western Pacific, IV-drug abuser	B-cell lymphoma	H	E2	HCV NAT, HCV treatment, clinical follow-up
									Marginal zone lymphoma	H	unknown or NS3, E7	
									MALT	H	NS3, E7	
									HCC	E	FNDC38	

Virus	Genome	Replication	Transmission	Cellular tropism	Primary infection	Screening of infection	Prevention	Population infected and regional prevalence	Malignancy	Type	Oncogenic viral particle; other mechanism	Recipient surveillance
HTLV 1	RNA, retrovirus, integrated in host genome; IARC 1	reverse transcriptase copies RNA into double-stranded DNA > integrated into host genome > replicated via cell as provirus	any fluid with cells, vertical	T lymphocyte	asymptomatic	serology	none	global <1 %; southwest Japan, sub-Saharan Africa, South America, Caribbean	adult T-cell leukaemia	H	Tax HBz	
Merkel MCPyV	circular double-stranded DNA, integrated in host genome IARC 2a	in nucleus: transcription by RNA polymerase of host > synthesis of viral proteins, release after sampling when cell dies	to be defined (possible: respiratory droplets, skin to skin)	epithelial cells of hair follicles, Merkel cells	asymptomatic	test to be defined	none	global 60-90 %	Merkel cell carcinoma	E	T large antigen, T small antigen	clinical follow-up
HPV	double-stranded DNA, integrated in host genome; IARC 1	in nucleus: transcription by DNA & RNA polymerase of host	sexually (mucosa contact); non-sexually skin to skin, vertical	stratified epithelial cells	warts, condyloma accuminata; oral/ laryngeal/ anal papillomatosis; cervical dysplasia	test to be defined, screening of skin/ cervix etc.	vaccination (4-valent: HPV-6, 11, 16, 18 or 9-valent: HPV-6, 11, 16, 18, 31, 33, 45, 52, 58), 'hygiene'	global 15 %; sub-Saharan Africa, East Asia, South America	cervical carcinoma	E	E6, genotype 16, 18	clinical follow-up
									Skin: basal and squamous cell carcinoma	E	E7	
									oropharyngeal squamous cell carcinoma	E	E7, genotype 16, 18 and 6, 11	
									squamous neoplasm of ocular surface	E	E7, many questions unresolved	

Table 9.6. **Risk of developing cancer and site of manifestation for common genes predisposing to cancer**

Affected gene	Genetic disorder	Sites of cancer and incidence/ relative risk (where known)
BAP1	BAP1 tumour predisposition syndrome	Melanoma; mesothelioma; uveal melanoma; renal cell carcinoma (RCC)
BRCA1		Breast (50-80 %); ovary (30-50 %); pancreas; colorectal; prostate
BRCA2		Melanoma; breast (50-80 %); pancreas (3-6 %); prostate (15 % by 65 years); ovary 10-25 %
	Carney complex	Myxoma in breast; malignant psammomatous melanocytic schwannoma; benign pituitary & adrenal tumours
	Carney triad	Gastric GIST; oesophageal leiomyoma; pulmonary chondroma; adrenocortical adenoma; paraganglionoma
	Carney-Stratakis syndrome	Gastric GST; paraganglionoma
CDH1		Breast (55 %, lobular); gastric (50-80 %); colorectal
CDKN2A		Melanoma (50-80 %); stomach; lung
	Cowden syndrome	Melanoma; breast (70-95 %); colorectal; follicular thyroid, uterus, RCC (17-50 %)
DICER1	DICER1 syndrome	Cervical PNET; sarcoma botryoides; Sertoli-Leydig ovarian tumour; pleuropulmonary blastoma (10-20 %); multinodular goitre; pituitary blastoma; embryonal rhabdomyosarcoma; Wilms tumour
FAP	Familial adenomatous polyposis	Colorectal (100 %); hepatoblastoma; duodenal polyps and cancer; papillary thyroid (1-12 %); desmoids
FLCN	Birt-Hogg-Dubé syndrome	Benign lung cysts; oncocytomas & RCC
Gorlin	Nevoid basal cell carcinoma syndrome	Basal cell carcinoma; medulloblastoma in children
HLRCC	Hereditary leiomyomatosis and renal cell cancer; Reed syndrome	Leiomyoma of skin; benign uterine fibroids; papillary carcinoma kidney (10-16 %)
	Hyperparathyroidism-jaw tumour syndrome	Parathyroid carcinoma (10-15 %); Wilms tumour; renal cysts & hamartomas
JPS	Juvenile polyposis syndrome	Melanoma (2-9 %); gastric cancer (21 %)
MAX		Phaeochomocytoma; paraganglionoma
MEN1	Multiple endocrine neoplasia type 1	Pancreatic endocrine (gastrinoma, VIPoma; glucagonoma); lung carcinoid; adrenocortical cancer (1 %); benign pituitary, parathyroid & meningioma
MEN2	Multiple endocrine neoplasia type 2	Medullary carcinoma thyroid (95-100 %); parathyroid adenoma; adrenal phaeochromocytoma (50 %)
MLH1/MSH2	Lynch syndrome	Sebaceous carcinomas of skin; colorectal, gastric, pancreatic, hepatobiliary, small bowel, uterus and ovary, adrenocortical, CNS, urothelial; leukaemia/lymphoma
MSH6	Lynch syndrome	As above
MUTYH	MUTYH associated polyposis	Stomach; polyposis/colorectal cancer (43-100 %); duodenal polyps and cancer (3-4 %)
NF1	Neurofibromatosis type 1	Breast (8 % by 50 years); malignant nerve sheath tumours; brain gliomas; leukaemia
NF2	Neurofibromatosis type 2	Benign fibroids; vestibular schwanomas; meningiomas; ependymomas
PALB2		Breast (33-58 %); pancreas (exocrine or endocrine); ovary
	Peutz-Jeghers	GI tract, pancreas, uterus, cervix, ovary, breast, testicular (Sertoli cell tumour)
PMS2	Lynch syndrome	Sebaceous carcinomas of skin; colorectal, gastric, pancreatic, hepatobiliary, small bowel, uterus and ovary, adrenocortical, CNS, urothelial; leukaemia/lymphoma
RAD51C	BROVCA3	Breast; ovary (10 %)
RAD51D		Ovary (10 %)
RB1		Melanoma; lung; retinoblastoma (90 %); osteosarcoma
SDHA	Succinate dehydrogenase complex subunit A	Phaeochromocytoma; paraganglionoma
SDHB	Succinate dehydrogenase complex subunit B	GIST; thyroid; phaeochomocytoma; paraganglionoma; RCC (14 % by 70 years)
SDHC	Succinate dehydrogenase complex subunit C	Phaeochomocytoma; paraganglionoma

Affected gene	Genetic disorder	Sites of cancer and incidence/ relative risk (where known)
SDHD	Succinate dehydrogenase complex subunit D	Phaeochomocytoma (71 % by 60 years); paraganglionoma (29 % by 60 years); RCC (8 % by 70 years)
TP53		Melanoma; squamous skin cancer; breast (50 %); pancreas; uterus; ovary; lung, adrenal cortex; bone & soft tissue sarcoma; RCC; leukaemia & lymphoma
VHL	Von Hippel–Lindau syndrome	Pancreatic neuro-endocrine tumours (5-17 %); phaeochromocytoma (10-20 %); benign retinal haemangioblastoma & haemangioblastoma in brain & spinal cord; RCC

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9.10. Tumour transmission in an organ recipient

9.10.1. Features suggesting tumour transmission

For the safety of other recipients of organs from the same donor, it is important to distinguish between donor-transmitted tumours, which are already present in the donor (detected or undetected) and transmitted to the recipient with the transplanted organ, and donor-derived tumours, which can develop from donor cells at any time after transplantation but were not present in the donor at the time of organ procurement (e.g. RCC in graft kidney 8 years after transplantation, some examples of post-transplant lympho-proliferative disorders/ PTLD). In some cases this distinction might be arbitrary (e.g. RCC arising 2 years after transplant).

Attention should be paid in cases of a lymphoma in a recipient after transplantation. Categorised simply as lymphoma, it can cover a lymphoid tumour arising in the recipient *de novo* (e.g. associated with Epstein–Barr virus) or represent a donor-transmitted lymphoma. Clarification should be attempted for the above-mentioned reasons.

Several events in the post-transplant period can raise the concern of a potentially transmitted donor tumour (see Table 9.1). These events may include donor malignancies diagnosed after transplantation, either by final pathologic examination or donor autopsy, signs or symptoms suspected of indicating malignancy transmission in the recipient, organ transplantation from a donor known or suspected to have transmitted malignancy to a separate recipient, or a new tumour diagnosis in a living donor shortly after donation.

Additional scenarios [273] that would raise reasonable suspicion of a possible donor-transmitted tumour include:

a. cancer (other than PTLD) arising within the first two years after transplant;
b. cancer arising in the allograft organ in a patient with no history of carcinoma in the corresponding native organ;
c. metastatic carcinoma arising in an allograft recipient, particularly when a primary site cannot be identified;
d. metastatic carcinoma of allograft type (e.g. RCC in a renal transplant recipient) in a recipient with no known history of that type of cancer;
e. CNS malignancy occurring outside the CNS, particularly in a transplant patient with no known CNS involvement;
f. sex-specific cancer (e.g. choriocarcinoma) arising in a male transplant patient [126];
g. age-discordant cancer (e.g. paediatric cancer arising in an adult transplant recipient, or vice versa);
h. cancer in which there is specific suspicion of donor origin (e.g. use of organs from a donor with a known history of cancer).

While most transmitted tumours appear within 24 months of transplantation, this is dependent on the unique doubling time of the specific tumour. There are case reports of aggressive tumours being diagnosed in the recipient > 5 years after transplantation [120, 121].

Clinical symptoms and signs of malignancy transmission are heterogeneous, depending on the type of tumour and organ transplanted. Usually, the transmitted malignancy is identifiable in the transplanted organ with or without extra-graft metastases, reflecting a tumour borne by the allograft. In other cases, the graft does not show evidence of malignant infiltration, which suggests that isolated tumour cells might be transmitted through the organ.

If recurrence of the recipient's primary disease (e.g. hepatocellular carcinoma) is suspected, be aware that such findings might also be a manifestation of metastases from a donor tumour [274]. In such cases, the possibility of a donor-transmitted tumour should be specifically raised with the pathologist.

A review of existing literature can often provide

insight into the expected frequency, most frequent manifestations and typical outcomes following treatment for many different transmitted tumour types. A curated collection of the literature is maintained by the Centro Nazionale Trapianti in association with OCATT/ONT and WHO, and is accessible at www.notifylibrary.org.

9.10.2. Managing recipients of organs from donors with tumours

Recipients who received organs from donors with a confirmed malignancy should be strictly followed to detect any transmission as early as possible. Investigation of graft dysfunction should also consider the possibility of transmission. No evidence-based guidance exists for post-transplant monitoring, which requires a difficult balance between the benefit of early detection and the harm of causing undue stress to the recipient as a result of over-investigation, particularly with tumours carrying a low transmission risk. That balance changes when there is diagnosis of a transmission event in the recipient of another organ from the same donor, or the diagnosis of tumour in a living donor.

No evidence-based policies currently exist to support amending the recipient's immunosuppressive protocol following transplantation of an organ from a donor with history of malignancy, in particular to an mTOR-based protocol. A number of clinical trials and epidemiologic studies have found the use of mTOR inhibitor-based immunosuppressant regimens in the recipient to be associated with reduced incidence of mainly *de novo* non-melanoma skin cancers [275-277], while the effects on other cancers are less well defined [278-280]. No long-term benefit of prophylactic mTOR treatment was found in reducing the incidence of hepatocellular carcinoma recurrence after liver transplantation in the large international prospective randomised SiLVER trial [281].

9.10.3. Managing suspected malignancy transmission

Transmission of a malignant tumour is considered a serious adverse reaction (SAR) in the recipient, and suspected transmission events require reporting to the assigned national Health Authority, together with investigation of such cases. These actions are mandatory in EU states according to Directive 2010/53/EU [12] (see Chapter 16).

In cases of suspected malignancy transmission from donor to recipient:

a. The Health Authority in charge of co-ordinating vigilance must be informed immediately, before further investigation or confirmation, to allow initiation of the appropriate precautionary actions to prevent harm to other recipients of organs from the same donor (see Chapter 16).
b. The recipient centres of organs from the same donor, as well as tissue organisations and the organ procurement organisation, should be alerted by the Health Authority in charge of co-ordinating vigilance, and the examination and a review process for this case started (e.g. *ad hoc* or standing expert committee). In the absence of such a Health Authority, an alternative procedure should be established to alert the recipient centres concerned.
c. Histologic examination of the recipient tumour and comparison of tumour tissue and recipient sex chromosomes (in the case of a sex-mismatched transplant) or other genetic or molecular features that would allow distinction of donor tissue from recipient tissue would be desirable to prove or exclude transmission of a donor malignancy. National law should be checked (e.g. consent requirements) prior to performing any DNA analysis of human tissue.

Close communication between centres and co-ordinating agencies/authorities (according to the administrative organisation of each setting) is necessary, not only for alerting other teams to a potential risk that should be carefully monitored, but also for determining the level of transmission in a lineage of recipients.

9.10.4. Tumour histology and genetic testing of donor and recipient

When a malignancy is detected, histology can provide the histotype of the tumour. Immunohistochemistry can help to identify a possible histogenesis, and molecular analysis can give information of donor or recipient origin. In the case of a tumour in one or more recipients transplanted with organs from a single donor, a morphological/immunohistochemical analysis of the tumour in the donor and the tumour arising in the recipients, or even comparison of the tumours arising in the separate recipients, can strongly imply donor origin if they are equivalent, even in the absence of molecular studies.

Different molecular cytogenetic methods are available for determining if a donor is the origin of a recipient tumour. They all work by comparing

tumour biopsy material with regular allograft material (containing donor DNA) against a sample of tumour-free recipient DNA [110]. In cases of a positive match between donor and tumour material (or mismatch between recipient and tumour material), donor origin is confirmed. Molecular cytogenetic methods include but are not limited to:

- Fluorescence *in situ* hybridisation (FISH). In cases of sex-mismatched recipients, this method indicates the presence of the XX or XY chromosome pair in a biopsy of the malignant tissue. Routinely processed paraffin-embedded tissue can be used.
- Microsatellite allelic analysis. This analysis permits distinction between individuals based on the genetic polymorphisms of repetitive DNA sequences. Routinely processed paraffin-embedded tissue can be used.
- Comparative genomic hybridisation (CGH). This method allows simultaneous comparison of all chromosomes in the genome, and can also be performed on routinely processed tissue.

9.10.5. Management of confirmed tumour transmission

When tumour transmission has been confirmed, physicians must discuss and decide on the options for intervention, taking into account the wishes of the recipient.

For recipients of heterotopic transplants like kidney and pancreas, withdrawal of immunosuppression followed by removal of the rejecting organ, with a return to dialysis and/or re-substitution of insulin has been successful in some cases in promoting rejection of residual tumour cells [9, 57, 89, 207, 282].

For recipients of orthotopic transplants such as liver, heart and lung, retransplantation has been considered when tumour-free survival of the recipient is likely [167, 283, 284], albeit knowing that this might not eliminate the transmitted tumour [112, 113], even when performed within a few days of realisation that a donor cancer may be present [88].

After lowering or completely withdrawing immunosuppression, it takes time until the immune system recovers and can potentially reject allogenic tumour cells. Other forms of immunomodulation have been shown to be effective. Repeated therapy with interferon, allogeneic cells in tuberculin-purified protein derivative, and finally cytotoxic lymphocytes (CTLs) primed against donor HLA, were used to clear residual metastatic melanoma which was resistant to graft nephrectomy and immunosuppression withdrawal in one report [108]. Such observations suggest that chimeric antigen receptor (CAR)-T cells, and other novel immunomodulatory agents, may have a role in treating donor cancers resistant to immunosuppression withdrawal, or in heterotopic transplants following retransplantation where immunosuppression cannot be completely withdrawn. Systemic spread of a transmitted tumour could be treated by chemotherapy or appropriate targeted therapy according to the tumour type if immunotherapy is not possible.

All other recipients of grafts from the same donor, as well as the organ procurement organisation, allocation agencies and tissue establishments involved, have to be informed immediately so that they can initiate diagnostics and consider the possibility of prophylactic transplant removal, retransplantation or other intervention. Whether or not other grafts from the same donor that are currently not affected by the tumour should be removed requires careful assessment and will depend on the kind of malignancy and the clinical condition of the recipient.

9.10.6. Perspectives for data reporting and recording

National expert committees should be put in place to review reports of suspected transmission cases [5]. In the countries of the EU, a final report of each case has to be prepared after a defined period of 3 months [12] (see Chapter 16). Since this is a very short period for malignancy follow-up, long-term surveillance of the respective recipients at risk is preferred for at least 5 years.

In order to better inform decisions in the use of organs from donors with a history of cancer, and to inform treatment strategies for recipients who develop transmitted cancers, it is important to record all cases of tumour transmission. Transplant tumour registries should be established in every country or allocation network (e.g. Eurotransplant) as part of the governance of transplantation, and international consensus should be sought on the data to be recorded, with a view to eventually facilitating interlinked registries.

9.11. Conclusions

A history of malignancy or, in some cases, an active malignant disease in the potential donor should not automatically be a veto to organ donation. The estimated risk of tumour transmission should be balanced against the benefit of the transplant for the designated recipients. The available literature consists of retrospective series with limited background

information and many case reports. Taken as a whole, the reported transmission rates are low (though high for some aggressive and advanced tumours) and the overall results are encouraging, although this may reflect a high degree of selection. Nevertheless, to allow a more evidence-based decision process, it will be necessary to collect detailed international data including reliable reporting of transmission events. A comprehensive traceability system with details of management of adverse events is essential.

Prerequisites for the individual acceptance of such organs should be a review of the detailed history of the donor malignancy and its management, and the informed consent of the organ recipients. The frequently urgent nature of organ transplantation often precludes the possibility of obtaining all of the desired information, and the physician must weigh available clinical data and published experience along with the medical condition and desires of the patient in arriving at the best possible decision. Although a certain transmission risk will remain in many cases, selected patients on the waiting lists will benefit from these organs in times of organ shortage.

Research agenda

From the literature and discussion of the available evidence, several topics have been identified for which evidence is inconsistent, insufficient or non-existent. The authors of this guide recommend that future research, where possible in well-designed randomised clinical trials, should focus on the following research gaps:

1 Standardised reporting to national health services of transmission events, treatments and outcomes, to enable collation of incidences and outcomes for different cancer types.
2 Evaluation of modifying immunosuppression to include an mTOR inhibitor when transplanting an organ from a donor with a history of malignancy.
3 Evaluation of policy of watchful waiting *versus* aggressive follow-up monitoring of patients who have received an organ from a donor with a history of malignancy.
4 Exploration of immune therapies such as CAR-T cells in the treatment of transmitted tumours.

9.12. References

1. Murray J, Gleason R and Bartholomay A. Fourth Report of the Human Kidney Transplant Registry: 16 September 1964 to 15 March 1965. *Transplantation* 1965;3(5):684-99.
2. McPhaul JJ and McIntosh DA. Tissue transplantation still vexes. *N Engl J Med* 1965;272(2):105.
3. Penn I. Primary kidney tumors before and after renal transplantation. *Transplantation* 1995;59(4):480-5.
4. Penn I. Transmission of cancer from organ donors. *Ann Transplantation* 1997;2(4):7-12.
5. Ison MG and Nalesnik MA. An update on donor-derived disease transmission in organ transplantation. *Am J Transplantation* 2011;11(6):1123-30.
6. Desai R, Collett D, Watson CJ *et al.* Cancer transmission from organ donors – unavoidable but low risk. *Transplantation* 2012;94(12):1200-07.
7. Garrido G and Matesanz R. The Spanish National Transplant Organization (ONT) tumor registry. *Transplantation* 2008;85(8 Suppl):S61-3.
8. Nalesnik MA, Woodle ES, Dimaio JM *et al.* Donor-transmitted malignancies in organ transplantation: assessment of clinical risk. *Am J Transplantation* 2011;11(6):1140-7.
9. Moench K, Breidenbach T, Fischer-Fröhlich C-L *et al.* 6-year survey of organ donors with malignancies in Germany. *Transplantation* 2012;94(10S):527.
10. Lopez-Navidad A and Caballero F. Extended criteria for organ acceptance. Strategies for achieving organ safety and for increasing organ pool. *Clin Transplant* 2003;17(4):308-24.
11. SaBTO (Advisory Committee on the Safety of Blood, Tissues and Organs). Transplantation of organs from deceased donors with cancer or a history of cancer. London: Department of Health 2014 [updated 24 December 2020]; available at www.gov.uk/government/publications/transplantation-of-organs-from-donors-with-a-history-of-cancer, accessed 11 June 2021.
12. European Parliament and Council. Directive 2010/53/EU on standards of quality and safety of human organs intended for transplantation. Brussels: EU Publications Office, 7 July 2010.
13. Eccher A, Cima L, Ciangherotti A *et al.* Rapid screening for malignancy in organ donors: 15-year experience with the Verona "Alert" protocol and review of the literature. *Clin Transplant* 2017;31(9). https://doi.org/10.1111/ctr.13045.
14. Fiorentino M, D'Errico A, Corti B *et al.* A multiorgan donor cancer screening protocol: the Italian Emilia-Romagna region experience. *Transplantation* 2003;76(12):1695-9.
15. Zucchini N, Fiorentino M, D'Errico Grigioni A *et al.* The Italian multiorgan donor cancer screening protocol: 2002-2005 experience. *Transplantation* 2008;85(8 Suppl):S57-60.
16. O'Neill DC, Davis NF, Murray TE *et al.* Prevalence of incidental findings on multidetector computed tomography in potential nephrectomy donors: a prospective observational study. *Exp Clin Transplant* 2019;17(2):177-82.
17. Königsrainer A. Transmission of non-Hodgkin's lymphoma through renal allografts – disastrous result of

false diagnosis and inadequate information. *Transplant Proc* 1993;25(6):3075-6.

18. American Joint Committee on Cancer. *AJCC Cancer Staging Manual*, 8th edn 2016 [5/10/2019]; available at https://cancerstaging.org/Pages/default.aspx, accessed 11 June 2021.
19. Louis DN, Perry A, Reifenberger G *et al.* The 2016 World Health Organization Classification of tumors of the central nervous system: a summary. *Acta Neuropathol* 2016;131(6):803-20.
20. VanderWalde AM and Hurria A. Second malignancies among elderly survivors of cancer. *Oncologist* 2011;16(11):1572-81.
21. Deutsch M, Land SR, Begovic M *et al.* An association between postoperative radiotherapy for primary breast cancer in 11 National Surgical Adjuvant Breast and Bowel Project (NSABP) studies and the subsequent appearance of pleural mesothelioma. *Am J Clin Oncol* 2007;30(3):294-6.
22. Schaapveld M, Aleman BM, van Eggermond AM *et al.* Second cancer risk up to 40 years after treatment for Hodgkin's lymphoma. *N Engl J Med* 2015;373(26):2499-511.
23. Kauffman HM, McBride MA and Delmonico FL. First report of the United Network for Organ Sharing Transplant Tumor Registry: donors with a history of cancer. *Transplantation* 2000;70(12):1747-51.
24. Kauffman HM, McBride MA and Delmonico FL. UNOS Transplant Tumor Registry: donors with a history of cancer. *Transplant Proc* 2001;33(1-2):1844-5.
25. Kauffman HM, McBride MA, Cherikh WS *et al.* Transplant tumor registry: donor related malignancies. *Transplantation* 2002;74(3):358-62.
26. Kauffman HM, Cherikh WS, McBride MA *et al.* Deceased donors with a past history of malignancy: an organ procurement and transplantation network/united network for organ sharing update. *Transplantation* 2007;84(2):272-4.
27. Armanios MY, Grossman SA, Yang SC *et al.* Transmission of glioblastoma multiforme following bilateral lung transplantation from an affected donor: case study and review of the literature. *Neuro-Oncology* 2004;6(3):259-63.
28. Kauffman HM, McBride MA, Cherikh WS *et al.* Transplant tumor registry: donors with central nervous system tumors. *Transplantation* 2002;73(4):579-82.
29. Hynes CF, Ramakrishnan K, Alfares FA *et al.* Risk of tumor transmission after thoracic allograft transplantation from adult donors with central nervous system neoplasm – a UNOS database study. *Clin Transplant* 2017;31(4). https://doi.org/10.1111/ctr.12919.
30. Green M, Covington S, Taranto S *et al.* Donor-derived transmission events in 2013: a report of the Organ Procurement Transplant Network Ad Hoc Disease Transmission Advisory Committee. *Transplantation* 2015;99(2):282-7.
31. Feng S, Buell J, Cherikh W *et al.* Organ donors with positive viral serology or malignancy: risk of disease transmission by transplantation. *Transplantation* 2002;74(12):1657-63.
32. Buell JF, Trofe J, Hanaway MJ *et al.* Transmission of donor cancer into cardiothoracic transplant recipients. *Surgery* 2001;130(4):660-66; discussion 666-8.
33. Buell JF, Trofe J, Sethuraman G *et al.* Donors with central nervous system malignancies: are they truly safe? *Transplantation* 2003;76(2):340-43.
34. Buell JF, Hanaway MJ, Thomas M *et al.* Donor kidneys with small renal cell cancers: can they be transplanted? *Transplant Proc* 2005;37(2):581-2.
35. Desai R, Collett D, Watson CJ *et al.* Estimated risk of cancer transmission from organ donor to graft recipient in a national transplantation registry. *Br J Surg* 2014;101(7):768-74.
36. Watson CJE, Roberts R, Wright KA *et al.* How safe is it to transplant organs from deceased donors with primary intracranial malignancy? An analysis of UK Registry data. *Am J Transplant* 2010;10(6):1437-44.
37. Venettoni S, Emilio SC, Scalamogna M *et al.* Strategies for evaluation of suitable donors: Italian experience. *Ann Transplant* 2004;9(2):15-16.
38. Nanni Costa A, Grossi P, Gianelli Castiglione A *et al.* Quality and safety in the Italian donor evaluation process. *Transplantation* 2008;85(8 Suppl):S52-6.
39. Taioli E, Mattucci DA, Palmieri S *et al.* A population-based study of cancer incidence in solid organ transplants from donors at various risk of neoplasia. *Transplantation* 2007;83(1):13-16.
40. Fiaschetti P, Pretagostini R, Stabile D *et al.* The use of neoplastic donors to increase the donor pool. *Transplant Proc* 2012;44(7):1848-50.
41. Eccher A, Lombardini L, Girolami I *et al.* How safe are organs from deceased donors with neoplasia? The results of the Italian Transplantation Network. *J Nephrol* 2019;32(2):323-30.
42. Birkeland SA and Storm HH. Risk for tumor and other disease transmission by transplantation: a population-based study of unrecognized malignancies and other diseases in organ donors. *Transplantation* 2002;74(10):1409-13.
43. Mulder SA, Kranse R, Damhuis RA *et al.* The incidence and risk factors of metachronous colorectal cancer: an indication for follow-up. *Dis Colon Rectum* 2012;55(5):522-31.
44. Nalesnik M and Ison M. Organ transplantation from deceased donors with cancer: is it safe? *Open Access Surgery* 2011;4:11-20.
45. Franken B, de Groot MR, Mastboom WJ *et al.*

Circulating tumor cells, disease recurrence and survival in newly diagnosed breast cancer. *Breast Cancer Res* 2012;14(5):R133.

46. van Dalum G, van der Stam GJ, Tibbe AG *et al.* Circulating tumor cells before and during follow-up after breast cancer surgery. *Int J Oncol* 2015;46(1):407-13.
47. Loh J, Jovanovic L, Lehman M *et al.* Circulating tumor cell detection in high-risk non-metastatic prostate cancer. *J Cancer Res Clin Oncol* 2014;140(12):2157-62.
48. Muller C, Holtschmidt J, Auer M *et al.* Hematogenous dissemination of glioblastoma multiforme. *Sci Transl Med* 2014;6(247):247ra101. https://doi.org/10.1126/scitranslmed.3009095.
49. Tang J, Flomenberg P, Harshyne L *et al.* Glioblastoma patients exhibit circulating tumor-specific CD8+ T cells. *Clin Cancer Res* 2005;11(14):5292-9.
50. Coumans FA, Ligthart ST, Uhr JW *et al.* Challenges in the enumeration and phenotyping of CTC. *Clin Cancer Res* 2012;18(20):5711-18.
51. Fischer C, Haque SS, Huse JT *et al.* Extraneural ependymoma: distant bone, lung, liver, and lymph node metastases following bevacizumab. *Pediatr Blood Cancer* 2013;60(1):143-5.
52. Organización Nacional de Trasplantes. Criterios para prevenir la transmisión de enfermedades neoplásicas en la donación de órganos. Madrid: ONT 2006.
53. Organ Procurement and Transplantation Network, Policy 15.5.A: Transplant program requirements for communicating post-transplant discovery of disease or malignancy. *OPTN Policies*, 2021,312, available at https://optn.transplant.hrsa.gov/governance/policies, accessed 11 June 2021.
54. Ferlay J, Colombet M, Soerjomataram I *et al.* Cancer incidence and mortality patterns in Europe: Estimates for 40 countries and 25 major cancers in 2018. *Eur J Cancer* 2018;103:356-87.
55. Moertel CG, Weiland LH, Nagorney DM *et al.* Carcinoid tumor of the appendix: treatment and prognosis. *N Engl J Med* 1987;317(27):1699-701.
56. Landry CS, Woodall C, Scoggins CR *et al.* Analysis of 900 appendiceal carcinoid tumors for a proposed predictive staging system. *Arch Surg* 2008;143(7):664-70; discussion 670.
57. Friedman A, Muthiah C, Beebe T *et al.* Collective experience with renal transplantation from donors with a history of breast cancer. *Am J Transplant* 2003;3(S5):288-9.
58. Buell JF, Beebe TM, Trofe J *et al.* Donor transmitted malignancies. *Ann Transplant* 2004;9(1):53-6.
59. Matser YAH, Terpstra ML, Nadalin S *et al.* Transmission of breast cancer by a single multiorgan donor to 4 transplant recipients. *Am J Transplant* 2018;18(7):1810-14.
60. Miller AK, Young JW, Wilson DJ *et al.* Transmission of donor-derived breast carcinoma as a recurrent mass in a keratolimbal allograft. *Cornea* 2017;36(6):736-9.
61. Gomis RR and Gawrzak S. Tumor cell dormancy. *Mol Oncol* 2017;11(1):62-78.
62. Dittmer J, Mechanisms governing metastatic dormancy in breast cancer. *Semin Cancer Biol* 2017;44:72-82.
63. Albert JM, Gonzalez-Angulo AM, Guray M *et al.* Estrogen/progesterone receptor negativity and HER2 positivity predict locoregional recurrence in patients with T1a,bNo breast cancer. *Int J Radiat Oncol Biol Phys* 2010;77(5):1296-302.
64. Palmieri D, Bronder JL, Herring JM *et al.* Her-2 overexpression increases the metastatic outgrowth of breast cancer cells in the brain. *Cancer Res* 2007;67(9):4190-98.
65. Benson JR and Wishart GC. Predictors of recurrence for ductal carcinoma *in situ* after breast-conserving surgery. *Lancet Oncol* 2013;14(9):e348-57.
66. Lagios MD, Margolin FR, Westdahl PR *et al.* Mammographically detected duct carcinoma *in situ*. Frequency of local recurrence following tylectomy and prognostic effect of nuclear grade on local recurrence. *Cancer* 1989;63(4):618-24.
67. Fisher ER, Land SR, Fisher B *et al.* Pathologic findings from the National Surgical Adjuvant Breast and Bowel Project: twelve-year observations concerning lobular carcinoma *in situ*. *Cancer* 2004;100(2):238-44.
68. Feng S, Buell JF, Chari RS *et al.* Tumors and transplantation: The 2003 Third Annual ASTS State-of-the-Art Winter Symposium. *Am J Transplant* 2003;3(12):1481-7.
69. Landow SM, Gjelsvik A and Weinstock MA. Mortality burden and prognosis of thin melanomas overall and by subcategory of thickness, SEER registry data, 1992-2013. *J Am Acad Dermatol* 2017;76(2):258-63.
70. Braun-Parvez L, Charlin E, Caillard S *et al.* Gestational choriocarcinoma transmission following multiorgan donation. *Am J Transplant* 2010;10(11):2541-6.
71. Xiao D, Craig JC, Chapman JR *et al.* Donor cancer transmission in kidney transplantation: a systematic review. *Am J Transplant* 2013;13(10):2645-52.
72. Snape K, Izatt L, Ross P *et al.* Donor-transmitted malignancy confirmed by quantitative fluorescence polymerase chain reaction genotype analysis: a rare indication for liver retransplantation. *Liver Transplant* 2008;14(2):155-8.
73. Zelinkova Z, Geurts-Giele I, Verheij J *et al.* Donor-transmitted metastasis of colorectal carcinoma in a transplanted liver. *Transpl Int* 2012;25(1):e10-15.
74. Bouvier AM, Latournerie M, Jooste V *et al.* The lifelong risk of metachronous colorectal cancer justifies long-term colonoscopic follow-up. *Eur J Cancer* 2008;44(4):522-7.

75. Yamacake KG, Antonopoulos IM, Piovesan AC *et al.* Donor transmission intestinal carcinoma after kidney transplantation: case report. *Transplant Proc* 2015; 47(3):827-30.
76. Beaton C, Twine CP, Williams GL *et al.* Systematic review and meta-analysis of histopathological factors influencing the risk of lymph node metastasis in early colorectal cancer. *Colorectal Dis* 2013;15(7):788-97.
77. Mou S, Soetikno R, Shimoda T *et al.* Pathologic predictive factors for lymph node metastasis in submucosal invasive (T1) colorectal cancer: a systematic review and meta-analysis. *Surg Endosc* 2013;27(8): 2692-703.
78. Kang J, Lee HW, Kim IK *et al.* Clinical implications of microsatellite instability in T1 colorectal cancer. *Yonsei Med J* 2015;56(1):175-81.
79. ESMO/European Sarcoma Network Working Group. Gastrointestinal stromal tumours: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 2014;25 Suppl 3:iii21-6.
80. Joensuu H, Vehtari A, Riihimaki J *et al.* Risk of recurrence of gastrointestinal stromal tumour after surgery: an analysis of pooled population-based cohorts. *Lancet Oncol* 2012;13(3):265-74.
81. Novelli L, Messerini L, Caporalini C *et al.* Gastrointestinal stromal tumor diagnosed during donor procurement: the experience of a single institution and review of the literature. *Med Sci Tech* 2017;58:62-6.
82. Forbes GB, Goggin MJ, Dische FE *et al.* Accidental transplantation of bronchial carcinoma from a cadaver donor to two recipients of renal allografts. *J Clin Pathol* 1981;34(2):109-15.
83. Göbel H, Gloy J, Neumann J *et al.* Donor-derived small cell lung carcinoma in a transplanted kidney. *Transplantation* 2007;84(6):800-02.
84. Bodvarsson S, Burlingham W, Kusaka S *et al.* Donor-derived small cell lung carcinoma in a kidney transplant recipient. *Cancer* 2001;92(9):2429-34.
85. Winter TC, Keller PR, Lee Jr FT *et al.* Donor-derived malignancy: transmission of small-cell lung cancer via renal transplantation. *Ultrasound Med* 2001;20(5): 559-62.
86. Sonbol MB, Halling KC, Douglas DD *et al.* A case of donor-transmitted non-small cell lung cancer after liver transplantation: an unwelcome guest. *Oncologist* 2019;24(6):e391-3.
87. Jaillard A, Baillet C, Beron A *et al.* FDG PET/CT allowing detection and follow-up of tumor cell transplantation. *Ann Nucl Med* 2016;30(3):250-54.
88. Lipshutz GS, Baxter-Lowe LA, Nguyen T *et al.* Death from donor-transmitted malignancy despite emergency liver retransplantation. *Liver Transplant* 2003; 9(10):1102-7.
89. Chen KT, Olszanski A and Farma JM. Donor transmission of melanoma following renal transplant. *Case Rep Transplant* 2012;2012:764019.
90. Cankovic M, Linden MD and Zarbo RJ. Use of microsatellite analysis in detection of tumor lineage as a cause of death in a liver transplant patient. *Arch Pathol Lab Med* 2006;130(4):529-32.
91. Morris-Stiff G, Steel A, Savage P *et al.* Transmission of donor melanoma to multiple organ transplant recipients. *Am J Transplant* 2004;4(3):444-6.
92. Singh P, Pandey D, Rovin B *et al.* Successful treatment and five years of disease-free survival in a donor transmitted metastatic melanoma with ipilimumab therapy. *Cureus* 2019;11(5):e4658.
93. Strauss DC and Thomas JM. Transmission of donor melanoma by organ transplantation. *Lancet Oncol* 2010;11(8):790-96.
94. Alsara A and Rafi M. Donor-transmitted melanoma after limbal stem cell transplantation. *Avicenna J Med* 2017;7(2):75-7.
95. Sepsakos L, Cheung AY, Nerad JA *et al.* Donor-derived conjunctival-limbal melanoma after a keratolimbal allograft. *Cornea* 2017;36(11):1415-18.
96. Li J, EBAA (Eye Bank Association of America). Major guidance and standards changes. *Int J Eye Bank* 2016; 4(2):1-3.
97. EDQM, *Guide to the quality and safety of tissues and cells for human application*, 5th edn. Strasbourg: Council of Europe 2022.
98. EEBA (European Eye Bank Association). Minimum medical standards. Venice: EEBA 2016.
99. Pierard-Franchimont C, Hermanns-Le T, Delvenne P *et al.* Dormancy of growth-stunted malignant melanoma: sustainable and smoldering patterns. *Oncol Rev* 2014;8(2):252.
100. Tseng WW, Fadaki N and Leong SP. Metastatic tumor dormancy in cutaneous melanoma: does surgery induce escape? *Cancers (Basel)* 2011;3(1):730-46.
101. Linde N, Fluegen G and Aguirre-Ghiso JA. The relationship between dormant cancer cells and their microenvironment. *Adv Cancer Res* 2016;132:45-71.
102. Tsao H, Cosimi AB and Sober AJ. Ultra-late recurrence (15 years or longer) of cutaneous melanoma. *Cancer* 1997;79(12):2361-70.
103. Kaliki S and Shields CL. Uveal melanoma: relatively rare but deadly cancer. *Eye (Lond)* 2017;31(2):241-57.
104. Carvajal RD, Schwartz GK, Tezel T *et al.* Metastatic disease from uveal melanoma: treatment options and future prospects. *Br J Ophthalmol* 2017;101(1):38-44.
105. Isaksson K, Mikiver R, Eriksson H *et al.* Survival in 31 670 patients with thin melanomas – a Swedish population-based study. *Br J Dermatol* 2020 (4 March), available at https://doi.org/10.1111/bjd.19015.
106. Lo SN, Scolyer RA and Thompson JF. Long-term survival of patients with thin (T1) cutaneous melanomas:

a Breslow thickness cut point of 0.8 mm separates higher-risk and lower-risk tumors. *Ann Surg Oncol* 2018;25(4):894-902.

107. Boyle SM, Ali N, Olszanski AJ *et al.* Donor-derived metastatic melanoma and checkpoint inhibition. *Transplant Proc* 2017;49(7):1551-4.
108. Suranyi MG, Hogan PG, Falk MC *et al.* Advanced donor-origin melanoma in a renal transplant recipient: immunotherapy, cure, and retransplantation. *Transplantation* 1998;66(5):655-61.
109. Schroettner P, Gruellich C, Hasskarl J *et al.* Achievement of a continuous complete remission in a kidney transplant patient with advanced donor-derived small cell carcinoma. *Transplantation* 2010;90(1):94-5.
110. Baehner R, Magrane G, Balassanian R *et al.* Donor origin of neuroendocrine carcinoma in 2 transplant patients determined by molecular cytogenetics. *Human Pathology* 2000;31(11):1425-9.
111. Foltys D, Linkermann A, Heumann A *et al.* Organ recipients suffering from undifferentiated neuroendocrine small-cell carcinoma of donor origin: a case report. *Transplant Proc* 2009;41(6):2639-42.
112. Begum R, Harnois D, Satyanarayana R *et al.* Retransplantation for donor-derived neuroendocrine tumor. *Liver Transpl* 2011;17(1):83-7.
113. Al-Azzawi Y, Stein LL, Shrestha R *et al.* Donor-derived hepatic neuroendocrine tumor: pause before proceeding with liver retransplantation. *Transplant Direct* 2016;2(7):e88.
114. Mrzljak A, Kocman B, Skrtic A *et al.* Liver re-transplantation for donor-derived neuroendocrine tumor: A case report. *World J Clin Cases* 2019;7(18):2794-2801.
115. Szalat A, Fraenkel M, Doviner V *et al.* Malignant pheochromocytoma: predictive factors of malignancy and clinical course in 16 patients at a single tertiary medical center. *Endocrine* 2011;39(2):160-6.
116. Linnoila RI, Keiser HR, Steinberg SM *et al.* Histopathology of benign versus malignant sympathoadrenal paragangliomas: clinicopathologic study of 120 cases including unusual histologic features. *Hum Pathol* 1990;21(11):1168-80.
117. Thompson LD. Pheochromocytoma of the Adrenal gland Scaled Score (PASS) to separate benign from malignant neoplasms: a clinicopathologic and immunophenotypic study of 100 cases. *Am J Surg Pathol* 2002;26(5):551-66.
118. Pham TH, Moir C, Thompson GB *et al.* Pheochromocytoma and paraganglioma in children: a review of medical and surgical management at a tertiary care center. *Pediatrics* 2006;118(3):1109-17.
119. Abdalla AH, Rassoul Z, Mousa DH *et al.* A pheochromocytoma in a cadaver kidney donor: to transplant or not to transplant? *Nephrol Dial Transplant* 1996;11(10): 2080-82.
120. Sharma S, Wray C and Nourmand H. Anesthetic management for resection of hepatic paraganglioma metastatic from the donor organ in an orthotopic liver transplant recipient: a case report. *Transplant Proc* 2013;45(2):817-19.
121. Yang SE, Kim C, Wang H *et al.* RE: Anesthetic management for resection of hepatic paraganglioma metastatic from the donor organ in an orthotopic liver transplant recipient: a case report. *Transplant Proc* 2015;47(6):2072-3.
122. Fujiwara T, Sakuma Y, Hosoya Y *et al.* Liver transplantation from a living donor with early gastric cancer. *Am J Transplant* 2005;5(3):627-9.
123. Gerstenkorn C and Thomusch O. Transmission of a pancreatic adenocarcinoma to a renal transplant recipient. *Clin Transplant* 2003;17(5):473-6.
124. Georgieva LA, Gielis EM, Hellemans R *et al.* Single-center case series of donor-related malignancies: rare cases with tremendous impact. *Transplant Proc* 2016;48(8):2669-77.
125. Matsukuma KE and Yeh MM. Update on the pathology of liver neoplasms. *Ann Diagn Pathol* 2019;38: 126-37.
126. Lipshutz GS, Mihara N, Wong R *et al.* Death from metastatic donor-derived ovarian cancer in a male kidney transplant recipient. *Am J Transplant* 2009; 9(2):428-32.
127. Nickkholgh A, Frey E, Krenzel C *et al.* The need for vigilance in extended criteria donors with a past history of malignancy: a case report and review of literature. *Ann Transplant* 2011;16(1):75-9.
128. Sanchez-Chapado M, Olmedilla G, Cabeza M *et al.* Prevalence of prostate cancer and prostatic intraepithelial neoplasia in Caucasian Mediterranean males: an autopsy study. *Prostate* 2003;54(3):238-47.
129. Yin M, Bastacky S, Chandran U *et al.* Prevalence of incidental prostate cancer in the general population: a study of healthy organ donors. *J Urol* 2008; 179(3):892-5; discussion 895. https://doi.org/10.1016/j.juro.2007.10.057.
130. Frutos MA, Daga D, Ruiz P *et al.* Prostate-specific antigen in the assessment of organ donors. *Transplant Proc* 2003;35(5):1644-6.
131. Pabisiak K, Ostrowski M, Kram A *et al.* Prostate-specific antigen: nonspecific in deceased organ donors. *Transplant Proc* 2016;48(5):1374-7.
132. Skalski M, Gierej B, Nazarewski L *et al.* Prostate cancer in deceased organ donors: loss of organ or transplantation with active surveillance. *Transplant Proc* 2018;50(7):1982-4.
133. Gleason DF. Histologic grading of prostate cancer: a perspective. *Hum Pathol* 1992;23(3):273-9.
134. Egevad L, Delahunt B, Evans AJ *et al.* International

Society of Urological Pathology (ISUP) grading of prostate cancer. *Am J Surg Pathol* 2016;40(6):858-61.

135. Mottet N, van den Bergh R, Briers E *et al.* EAU Guidelines: *Prostate cancer.* Arnhem: European Association of Urology 2019.
136. Neal DE, Metcalfe C, Donovan JL *et al.* Ten-year mortality, disease progression, and treatment-related side effects in men with localised prostate cancer from the ProtecT randomised controlled trial according to treatment received. *Eur Urol* 2020;77(3):320-30.
137. D'Errico-Grigioni A, Fiorentino M, Vasuri F *et al.* Expanding the criteria of organ procurement from donors with prostate cancer: the application of the new Italian guidelines. *Am J Transplant* 2010;10(8): 1907-11.
138. Doerfler A, Tillou X, Le Gal S *et al.* Prostate cancer in deceased organ donors: a review. *Transplant Rev (Orlando)* 2014;28(1):1-5.
139. Dholakia S, Johns R, Muirhead L *et al.* Renal donors with prostate cancer, no longer a reason to decline. *Transplant Rev (Orlando)* 2016;30(1):48-50.
140. Loh E, Couch FJ, Hendricksen C *et al.* Development of donor-derived prostate cancer in a recipient following orthotopic heart transplantation. *JAMA* 1997;277(2): 133-7.
141. Sanchez-Montes C, Aguilera V, Prieto M *et al.* Periesophageal lymph node metastasis of prostate adenocarcinoma from liver transplant donor. *Am J Gastroenterol* 2019;114(3):378.
142. Ljungberg B, Albiges L, Bensalah K *et al.* EAU Guidelines: *Renal cell carcinoma*. Arnhem: European Association of Urology 2019.
143. Van Poppel H, Da Pozzo L, Albrecht W *et al.* A prospective, randomised EORTC intergroup phase 3 study comparing the oncologic outcome of elective nephron-sparing surgery and radical nephrectomy for low-stage renal cell carcinoma. *Eur Urol* 2011;59(4): 543-52.
144. Hevia V, Hassan Zakri R, Fraser Taylor C *et al.* Effectiveness and harms of using kidneys with small renal tumors from deceased or living donors as a source of renal transplantation: a systematic review. *Eur Urol Focus* 2019;5(3):508-17.
145. Yu N, Fu S, Fu Z *et al.* Allotransplanting donor kidneys after resection of a small renal cancer or contralateral healthy kidneys from cadaveric donors with unilateral renal cancer: a systematic review. *Clin Transplant* 2014;28(1):8-15.
146. Pavlakis M, Michaels MG, Tlusty S *et al.* Renal cell carcinoma suspected at time of organ donation 2008-2016: a report of the OPTN *ad hoc* Disease Transmission Advisory Committee Registry. *Clin Transplant* 2019;33(7):e13597.
147. Lugo-Baruqui JA, Guerra G, Chen L *et al.* Living donor renal transplantation with incidental renal cell carcinoma from donor allograft. *Transplant Int* 2015; 28(9):1126-30.
148. Ogawa Y, Kojima K, Mannami M *et al.* Transplantation of restored kidneys from unrelated donors after resection of renal cell carcinoma: results from 10 patients. *Transplant Proc* 2015;47:1711-19.
149. Nicol DL, Preston JM, Wall DR *et al.* Kidneys from patients with small renal tumours: a novel source of kidneys for transplantation. *BJU Int* 2008;102(2):188-92; discussion 192-3.
150. Flechner SM and Campbell SC. The use of kidneys with small renal tumors for transplantation: who is taking the risk? *Am J Transplant* 2012;12(1):48-54.
151. Finelli A, Ismaila N and Russo P. Management of small renal masses: American Society of Clinical Oncology clinical practice guideline summary. *J Oncol Pract* 2017;13(4):276-8.
152. Leibovich BC, Blute ML, Cheville JC *et al.* Prediction of progression after radical nephrectomy for patients with clear cell renal cell carcinoma: a stratification tool for prospective clinical trials. *Cancer* 2003;97(7): 1663-71.
153. Serralta AS, Orbis FC, Sanjuan FR *et al.* If the donor had an early-stage genitourinary carcinoma and the liver has already been implanted, should we perform the transplantectomy? *Liver Transplant* 2003;9(12): 1281-5.
154. Carver BS, Zibari GB, Venable DD *et al.* Renal cell carcinoma detected in a cadaveric donor after orthotopic liver and contralateral renal transplantation in two recipients: four-year follow-up. *Transplantation* 2001;71(9):1348-9.
155. Meyding-Lamade U, Krieger D, Schnabel P *et al.* Cerebral metastases of an allogenic renal cell carcinoma in a heart recipient without renal cell carcinoma. *J Neurol* 1996;243(5):425-7.
156. Sack FU, Lange R, Mehmanesh H *et al.* Transferral of extrathoracic donor neoplasm by the cardiac allograft. *J Heart Lung Transplant* 1997;16(3):298-301.
157. Barrou B, Bitker MO, Delcourt A *et al.* Fate of a renal tubulopapillary adenoma transmitted by an organ donor. *Transplantation* 2001;72(3):540-41.
158. Brok J, Lopez-Yurda M, Tinteren HV *et al.* Relapse of Wilms' tumour and detection methods: a retrospective analysis of the 2001 Renal Tumour Study Group – International Society of Paediatric Oncology Wilms' tumour protocol database. *Lancet Oncol* 2018;19(8): 1072-81.
159. Delahunt B, McKenney JK, Lohse CM *et al.* A novel grading system for clear cell renal cell carcinoma incorporating tumor necrosis. *Am J Surg Pathol* 2013; 37(3):311-22.
160. Warren AY and Harrison D. WHO/ISUP classification,

grading and pathological staging of renal cell carcinoma: standards and controversies. *World J Urol* 2018; 36(12):1913-26.

161. Delahunt B, Sika-Paotonu D, Bethwaite PB *et al.* Grading of clear cell renal cell carcinoma should be based on nucleolar prominence. *Am J Surg Pathol* 2011;35(8):1134-9.
162. Sika-Paotonu D, Bethwaite PB, McCredie MR *et al.* Nucleolar grade but not Fuhrman grade is applicable to papillary renal cell carcinoma. *Am J Surg Pathol* 2006;30(9):1091-6.
163. Moch H, Cubilla AL, Humphrey PA *et al.* The 2016 WHO Classification of tumours of the urinary system and male genital organs – Part A: Renal, penile, and testicular tumours. *Eur Urol* 2016;70(1):93-105.
164. Grimaldi G, Reuter V and Russo P. Bilateral non-familial renal cell carcinoma. *Ann Surg Oncol* 1998;5(6): 548-52.
165. Llamas F, Gallego E, Salinas J *et al.* Sarcomatoid renal cell carcinoma in a renal transplant recipient. *Transplant Proc* 2009;41:4422-4.
166. Ortiz JA, Manzarbeitia C, Noto KA *et al.* Extended survival by urgent liver retransplantation after using a first graft with metastasis from initially unrecognized donor sarcoma. *Am J Transplant* 2005;5(6):1559-61.
167. Kreisel D, Engels FH, Krupnick AS *et al.* Emergent lung retransplantation after discovery of two primary malignancies in the donor. *Transplantation* 2001; 71(12):1859-62.
168. Detry O, De Roover A, de Leval L *et al.* Transmission of an undiagnosed sarcoma to recipients of kidney and liver grafts procured in a non-heart beating donor. *Liver Transplant* 2005;11(6):696-9.
169. Thoning J, Liu Y, Bistrup C *et al.* Transmission of angiosarcomas from a common multiorgan donor to four transplant recipients. *Am J Transplant* 2013;13(1): 167-73.
170. Oerlemans MIJF, Groenewegen G, Vink A *et al.* Donor-derived testicular germ cell cancer in a heart transplant recipient. *JACC CardioOncol* 2021 Jun 15; 3(2):322-5.
171. Kollmannsberger C, Tandstad T, Bedard PL *et al.* Patterns of relapse in patients with clinical stage I testicular cancer managed with active surveillance. *J Clin Oncol* 2015;33(1):51-7.
172. Asa SL and Ezzat S. The epigenetic landscape of differentiated thyroid cancer. *Mol Cell Endocrinol* 2018; 469:3-10.
173. Kim JG. Molecular pathogenesis and targeted therapies in well-differentiated thyroid carcinoma. *Endocrinol Metab (Seoul)* 2014;29(3):211-16.
174. Benko T, Hoyer DP, Saner FH *et al.* Liver transplantation from donors with a history of malignancy: a single-center experience. *Transplant Direct* 2017;3(11): e224.
175. Huurman VA, Baranski AG, Groeneveld JH *et al.* Transfer of ureteral carcinoma in a transplanted kidney presenting by early stenosis of the proximal ureter. *Clin Transplant* 2008;22(6):847-50.
176. Ferreira GF, de Oliveira RA, Jorge LB *et al.* Urothelial carcinoma transmission via kidney transplantation. *Nephrol Dial Transplant* 2010;25(2):641-3.
177. Backes AN, Tannuri AC, de Mello ES *et al.* Transmission of clear cell tumor in a graft liver from cadaveric donor: case report. *Pediatr Transplant* 2012;16(8): E352-5.
178. Hevia V, Gomez V, Alvarez S *et al.* Transitional cell carcinoma of the kidney graft: an extremely uncommon presentation of tumor in renal transplant recipients. *Case Rep Transplant* 2013;2013:196528.
179. Mannami M, Mannami R, Mitsuhata N *et al.* Last resort for renal transplant recipients, 'restored kidneys' from living donors/patients. *Am J Transplant* 2008;8(4):811-18.
180. Mitsuhata N, Mannami M, Mannami R *et al.* Restored renal transplants from donors with distal ureteral carcinomas. *Am J Transplant* 2012;12(1):261.
181. Takahara S, Nakatani T, Yoshida K *et al.* Living unrelated kidney transplantation from a donor with ureteral cancer jeopardizes survival of donor and recipient. *Am J Transplant* 2008;8(11):2479.
182. Shariat SF, Palapattu GS, Amie GEl *et al.* Characteristics and outcomes of patients with carcinoma *in situ* only at radical cystectomy. *Urology* 2006;68(3):538-42.
183. Gassel AM, Westphal E, Hansmann ML *et al.* Malignant lymphoma of donor origin after renal transplantation: a case report. *Hum Pathol* 1991;22(12): 1291-3.
184. Herzig KA, Falk MC, Jonsson JR *et al.* Novel surveillance and cure of a donor-transmitted lymphoma in a renal allograft recipient. *Transplantation* 2000;70(1): 149-52.
185. Harbell JW, Dunn TB, Fauda M *et al.* Transmission of anaplastic large cell lymphoma via organ donation after cardiac death. *Am J Transplant* 2008;8(1):238-44.
186. Dziewanowski K, Drozd R, Parczewski M *et al.* Multiorgan transplantation from a deceased donor with intravascular diffuse large B-cell lymphoma: transmission of the disease and results of treatment. *Clin Transplant* 2014;28(10):1080-83.
187. Kowal M, Hus M, Dmoszynska A *et al.* Acute T cell lymphoblastic leukemia in the recipient of a renal transplant from a donor with malignant lymphoma. *Acta Haematol* 2008;119(3):187-9.
188. Williams T, Aljitawi OS, Moussa R *et al.* First case of donor transmitted non-leukemic promyelocytic sarcoma. *Leuk Lymphoma* 2012;53(12):2530-34.

189. Sosin M, Nassif SR, Girlanda R *et al.* Isolated peritoneal donor-related plasmacytoma 3 years after liver transplantation: a case report. *Am J Transplant* 2014; 14(2):472-6.
190. Mouhieddine TH, Weeks LD and Ghobrial IM. Monoclonal gammopathy of undetermined significance. *Blood* 2019;133(23):2484-94.
191. Felldin M, Ekberg J, Polanska-Tamborek D *et al.* Donor monoclonal gammopathy may cause lymphoproliferative disorders in solid organ transplant recipients. *Am J Transplant* 2016;16(9):2676-83.
192. Serra N, Revuelta I, Blade J *et al.* Monoclonal gammopathy of undetermined significance: a contraindication for living kidney donation? *NDT Plus* 2011;4(4):256-7.
193. Arber DA, Orazi A, Hasserjian R *et al.* The 2016 revision to the World Health Organization classification of myeloid neoplasms and acute leukemia. *Blood* 2016; 127(20):2391-405.
194. Spivak JL. Myeloproliferative neoplasms. *N Engl J Med* 2017;377(9):895-6.
195. Barbui T, Barosi G, Birgegard G *et al.* Philadelphia-negative classical myeloproliferative neoplasms: critical concepts and management recommendations from European LeukemiaNet. *J Clin Oncol* 2011;29(6): 761-70.
196. DSO (Deutsche Stiftung Organtransplantation). Jahresbericht Organspende und Transplantation in Deutschland 2018 [Annual report on organ donation and transplantation in Germany, 2018]. Frankfurt am Main: DSO 2019.
197. Pasquier B, Pasquier D, N'Golet A *et al.* Extraneural metastases of astrocytomas and glioblastomas: clinicopathological study of two cases and review of literature. *Cancer* 1980;45(1):112-25.
198. Liwnicz BH and Rubinstein LJ. The pathways of extraneural spread in metastasizing gliomas: a report of three cases and critical review of the literature. *Hum Pathol* 1979;10(4):453-67.
199. Cavaliere R and Schiff D. Donor transmission of primary brain tumors: a neurooncologic perspective. *Transplant Rev* 2004;18(4):204-13.
200. Hoffman HJ and Duffner PK. Extraneural metastases of central nervous system tumors. *Cancer* 1985;56(7 Suppl):1778-82.
201. Ohgaki H and Kleihues P. Population-based studies on incidence survival rates and genetic alterations in astrocytic and oligodendroglial gliomas. *J Neuropathol Exp Neurol* 2005;64(6):479-89.
202. Detry O, Honore P, Hans MF *et al.* Organ donors with primary central nervous system tumor. *Transplantation* 2000;70(1):244-8; discussion 251-2.
203. Lefrancois N, Touraine JL, Cantarovich D *et al.* Transmission of medulloblastoma from cadaver donor to three organ transplant recipients. *Transplant Proc* 1987;19(1 Pt 3):2242.
204. Ruiz JC, Cotorruelo JG, Tudela V *et al.* Transmission of glioblastoma multiforme to two kidney transplant recipients from the same donor in the absence of ventricular shunt. *Transplantation* 1993;55(3):682-3.
205. Colquhoun SD, Robert ME, Shaked A *et al.* Transmission of CNS malignancy by organ transplantation. *Transplantation* 1994;57(6):970-74.
206. Jonas S, Bechstein WO, Lemmens HP *et al.* Liver graft-transmitted glioblastoma multiforme. A case report and experience with 13 multiorgan donors suffering from primary cerebral neoplasia. *Transpl Int* 1996;9(4):426-9.
207. Bosmans JL, Ysebaert D, De Cock AM *et al.* Interferon-alpha and the cure of metastasis of a malignant meningioma in a kidney allograft recipient: a case report. *Transplant Proc* 1997;29(1-2):838.
208. Frank S, Muller J, Bonk C *et al.* Transmission of glioblastoma multiforme through liver transplantation. *Lancet* 1998;352(9121):31.
209. Collignon FP, Holland EC and Feng S. Organ donors with malignant gliomas: an update. *Am J Transplant* 2004;4(1):15-21.
210. Kashyap R, Ryan C, Sharma R *et al.* Liver grafts from donors with central nervous system tumors: a single-center perspective. *Liver Transplant* 2009;15(10):1204-8.
211. Zhao P, Strohl A, Gonzalez C *et al.* Donor transmission of pineoblastoma in a two-yr-old male recipient of a multivisceral transplant: a case report. *Pediatr Transplant* 2012;16(4):E110-14.
212. Nauen DW and Li QK. Cytological diagnosis of metastatic glioblastoma in the pleural effusion of a lung transplant patient. *Diagn Cytopathol* 2014;42(7):619-23.
213. Val-Bernal F, Ruiz JC, Cotorruelo JG *et al.* Glioblastoma multiforme of donor origin after renal transplantation: report of a case. *Hum Pathol* 1993; 24(11):1256-9.
214. Fatt MA, Horton KM and Fishman EK. Transmission of metastatic glioblastoma multiforme from donor to lung transplant recipient. *J Comput Assist Tomogr* 2008;32(3):407-9.
215. Chen H, Shah AS, Girgis RE *et al.* Transmission of glioblastoma multiforme after bilateral lung transplantation. *J Clin Oncol* 2008;26(19):3284-5.
216. Perosa M, Crescentini F, Antunes I *et al.* Donor-derived malignancy in a pancreas graft. *Transpl Int* 2010;23(5):e5-6.
217. Morse JH, Turcotte JG, Merion RM *et al.* Development of a malignant tumor in a liver transplant graft procured from a donor with a cerebral neoplasm. *Transplantation* 1990;50(5):875-7.

218. Chui AK, Herbertt K, Wang LS *et al.* Risk of tumor transmission in transplantation from donors with primary brain tumors: an Australian and New Zealand registry report. *Transplant Proc* 1999;31(1-2):1266-7.

219. Pokorna E and Vitko S. The fate of recipients of organs from donors with diagnosis of primary brain tumor. *Transpl Int* 2001;14(5):346-7.

220. Warrens AN, Birch R, Collett D *et al.* Advising potential recipients on the use of organs from donors with primary central nervous system tumors. *Transplantation* 2012;93(4):348-53.

221. Detry O. Extended criteria donors: the case for liver procurement in donors with a central nervous system malignancy. *Liver Transplant* 2009;15(6):670-71.

222. Berger MS, Baumeister B, Geyer JR *et al.* The risks of metastases from shunting in children with primary central nervous system tumors. *J Neurosurg* 1991;74(6): 872-7.

223. Varan A, Sari N, Akalan N *et al.* Extraneural metastasis in intracranial tumors in children: the experience of a single center. *J Neurooncol* 2006;79(2):187-90.

224. Nikitovic M, Bokun J, Paripovic L *et al.* Bone metastases in medulloblastoma – single institution experience. *Pediatr Hematol Oncol* 2013;30(2):80-91.

225. Young RJ, Khakoo Y, Yhu S *et al.* Extraneural metastases of medulloblastoma: desmoplastic variants may have prolonged survival. *Pediatr Blood Cancer* 2015; 62(4):611-15.

226. Metellus P, Barrie M, Figarella-Branger D *et al.* Multicentric French study on adult intracranial ependymomas: prognostic factors analysis and therapeutic considerations from a cohort of 152 patients. *Brain* 2007;130(Pt 5):1338-49.

227. Pollack IF, Hurtt M, Pang D *et al.* Dissemination of low grade intracranial astrocytomas in children. *Cancer* 1994;73(11):2869-78.

228. Arulrajah S and Huisman TA. Pilomyxoid astrocytoma of the spinal cord with cerebrospinal fluid and peritoneal metastasis. *Neuropediatrics* 2008;39(4): 243-5.

229. Schroder R, Lorenzen J, Ostertag H *et al.* [Extraneural metastasis of brain and spinal cord tumors. Report of 2 cases]. *Pathologe* 1995;16(3):223-9.

230. Newton HB, Rosenblum MK and Walker RW. Extraneural metastases of infratentorial glioblastoma multiforme to the peritoneal cavity. *Cancer* 1992;69(8): 2149-53.

231. Awan M, Liu S, Sahgal A *et al.* Extra-CNS metastasis from glioblastoma: a rare clinical entity. *Expert Review of Anticancer Therapy* 2015;15(5):545-52.

232. Hornik L, Tenderich G, Wlost S *et al.* Organs from donors with primary brain malignancy: the fate of cardiac allograft recipients. *Transplant Proc* 2004; 36(10):3133-7.

233. Fecteau AH, Penn I and Hanto DW. Peritoneal metastasis of intracranial glioblastoma via a ventriculoperitoneal shunt preventing organ retrieval: case report and review of the literature. *Clin Transplant* 1998;12(4):348-50.

234. Cerame MA, Guthikonda M and Kohli CM. Extraneural metastases in gliosarcoma: a case report and review of the literature. *Neurosurgery* 1985;17(3):413-18.

235. Ostrom QT, Gittleman H, Farah P *et al.* CBTRUS statistical report: Primary brain and central nervous system tumors diagnosed in the United States in 2006-2010. *Neuro Oncol* 2013;15 Suppl 2:ii1-56.

236. Robertson T, Koszyca B and Gonzales M. Overview and recent advances in neuropathology. Part 1: Central nervous system tumours. *Pathology* 2011;43(2): 88-92.

237. Mazza E, Belli C, Terreni M *et al.* Breast metastases from oligodendroglioma: an unusual extraneural spread in two young women and a review of the literature. *Crit Rev Oncol Hematol* 2013;88(3):564-72.

238. Zustovich F, Della Puppa A, Scienza R *et al.* Metastatic oligodendrogliomas: a review of the literature and case report. *Acta Neurochir (Wien)* 2008;150(7): 699-702; discussion 702-3.

239. Davis MJ, Hasan F, Weinreb I *et al.* Extraventricular anaplastic ependymoma with metastasis to scalp and neck. *J Neurooncol* 2011;104(2):599-604.

240. Chao MM, Packer RJ, Myseros JS *et al.* Isolated extracranial recurrence of anaplastic ependymoma. *Pediatr Blood Cancer* 2011;56(2):317-18.

241. Kinoshita M, Izumoto S, Kagawa N *et al.* Long-term control of recurrent anaplastic ependymoma with extracranial metastasis: importance of multiple surgery and stereotactic radiosurgery procedures – case report. *Neurol Med Chir (Tokyo)* 2004;44(12):669-73.

242. Newton HB, Henson J and Walker RW. Extraneural metastases in ependymoma. *J Neurooncol* 1992;14(2): 135-42.

243. Perez-Bovet J, Rimbau-Munoz J and Martin-Ferrer S.. Anaplastic ependymoma with holocordal and intracranial meningeal carcinomatosis and holospinal bone metastases. *Neurosurgery* 2013;72(3):E497-503; discussion E503-4.

244. Schreiber D, Schneider J, Heller T *et al.* [Intracranial ependymoma with extraneural metastases]. *Zentralbl Allg Pathol* 1989;135(1):57-64.

245. Wakabayashi T, Yoshida J, Kuchiwaki H *et al.* [Extraneural metastases of malignant ependymoma inducing atelectasis and superior vena cava syndrome – a case report and review of the literature]. *No Shinkei Geka* 1986;14(1):59-65.

246. Alzahrani A, Alassiri A, Kashgari A *et al.* Extraneural metastasis of an ependymoma: a rare occurrence. *Neuroradiol J* 2014;27(2):175-8.

247. Hussain M, Mallucci C, Abernethy L *et al.* Anaplastic ependymoma with sclerotic bone metastases. *Pediatr Blood Cancer* 2010;55(6):1204-6.
248. Graf M, Blaeker H and Otto HF. Extraneural metastasizing ependymoma of the spinal cord. *Pathol Oncol Res* 1999;5(1):56-60.
249. Valladares JB, Perry RH and Kalbag RM. Malignant choroid plexus papilloma with extraneural metastasis. Case report. *J Neurosurg* 1980;52(2):251-5.
250. Lesoin F, Cama A, Dhellemmes P *et al.* Extraneural metastasis of a pineal tumor: report of 3 cases and review of the literature. *Eur Neurol* 1987;27(1):55-61.
251. Constantine C, Miller DC, Gardner S *et al.* Osseous metastasis of pineoblastoma: a case report and review of the literature. *J Neurooncol* 2005;74(1):53-7.
252. Charafe-Jauffret E, Lehmann G, Fauchon F *et al.* Vertebral metastases from pineoblastoma. *Arch Pathol Lab Med* 2001;125(7):939-43.
253. Jacobs JJ and Rosenberg AE. Extracranial skeletal metastasis from a pinealoblastoma: a case report and review of the literature. *Clin Orthop Relat Res* 1989(247):256-60.
254. Younis GA, Sawaya R, DeMonte F *et al.* Aggressive meningeal tumors: review of a series. *J Neurosurg* 1995;82(1):17-27.
255. Sato M, Matsushima Y, Taguchi J *et al.* [A case of intracranial malignant meningioma with extraneural metastases]. *No Shinkei Geka* 1995;23(7):633-7.
256. Lanfranchi M and Nikpoor N. Detection of meningioma metastasis to liver and lung using somatostatin receptor scintigraphy. *Clin Nucl Med* 2013;38(8):668-70.
257. Villanueva-Meyer JE, Magill ST, Lee JC *et al.* Detection of metastatic meningioma to the liver using 68Ga-DOTA-Octreotate PET/CT. *Clin Nucl Med* 2018; 43(9):e338-40.
258. Alexandru D, Glantz MJ, Kim L *et al.* Pulmonary metastases in patients with recurrent, treatment-resistant meningioma: prognosis and identification by 111-Indium-octreotide imaging. *Cancer* 2011;117(19):4506-11.
259. Scognamiglio G, D'Antonio A, Rossi G *et al.* CD90 expression in atypical meningiomas and meningioma metastasis. *Am J Clin Pathol* 2014;141(6):841-9.
260. Abboud M, Haddad G, Kattar M *et al.* Extraneural metastases from cranial meningioma: a case report. *Radiat Oncol* 2009;4:20.
261. Adlakha A, Rao K, Adlakha H *et al.* Meningioma metastatic to the lung. *Mayo Clin Proc* 1999;74(11):1129-33.
262. Kaminski JM, Movsas B, King E *et al.* Metastatic meningioma to the lung with multiple pleural metastases. *Am J Clin Oncol* 2001;24(6):579-82.
263. Perry A, Scheithauer BW and Nascimento AG. The immunophenotypic spectrum of meningeal hemangiopericytoma: a comparison with fibrous meningioma and solitary fibrous tumor of meninges. *Am J Surg Pathol* 1997;21(11):1354-60.
264. Kaneko T, Harada A, Isshiki K *et al.* Hemangiopericytomatous meningioma metastasized to the liver: report of a case and review of the literature. *Surg Today* 1993;23(7):644-8.
265. Suzuki H, Haga Y, Oguro K *et al.* Intracranial hemangiopericytoma with extracranial metastasis occurring after 22 years. *Neurol Med Chir (Tokyo)* 2002;42(7): 297-300.
266. Hoffman HJ, Yoshida M, Becker LE *et al.* Pineal region tumors in childhood: experience at the Hospital for Sick Children, 1983. *Pediatr Neurosurg* 1994; 21(1):91-103; discussion 104.
267. Yamagami T, Handa H, Takeuchi J *et al.* Choriocarcinoma arising from the pituitary fossa with extracranial metastasis: a review of the literature. *Surg Neurol* 1983;19(5):469-80.
268. Rutkowski MJ, Birk HS, Wood MD *et al.* Metastatic clival chordoma: a case report of multiple extraneural metastases following resection and proton beam radiotherapy in a 5-year old boy. *J Neurosurg Pediatr* 2017;19(5):531-7.
269. Harbell JW, Dunn TB, Fauda M *et al.* Transmission of anaplastic large cell lymphoma via organ donation after cardiac death. *Am J Transplant* 2008;8(1):238-44.
270. Mui UN, Haley CT and Tyring SK. Viral oncology: molecular biology and pathogenesis. *J Clin Med* 2017; 6(12).
271. Vélez-Bohórquez A, Bohórquez-Lozano M and Echeverry-de-Polanco M. The viruses in the human oncogenesis. *Infectio* 2018;22(4):213-22.
272. Lunn RM, Jahnke GD and Rabkin CS. Tumour virus epidemiology. *Philos Trans R Soc Lond B Biol Sci* 2017; 372(1732) 20160266.
273. Nalesnik MA. *Reporting post-transplant tumors to the OPTN*. DTAC news. 2010: OPTN/UNOS Ad Hoc Disease Transmission Advisory Committee.
274. Kim B, Woreta T, Chen PH *et al.* Donor-transmitted malignancy in a liver transplant recipient: a case report and review of literature. *Dig Dis Sci* 2013;58(5): 1185-90.
275. Yanik EL, Gustafson SK, Kasiske BL *et al.* Sirolimus use and cancer incidence among US kidney transplant recipients. *Am J Transplant* 2015;15(1):129-36.
276. Lim WH, Russ GR, Wong G *et al.* The risk of cancer in kidney transplant recipients may be reduced in those maintained on everolimus and reduced cyclosporine. *Kidney Int* 2017;91(4):954-63.
277. Dhakal P, Giri S, Siwakoti K *et al.* Renal cancer in recipients of kidney transplant. *Rare Tumors* 2017;9(1): 6550.
278. Alberu J, Pascoe MD, Campistol JM *et al.* Lower malignancy rates in renal allograft recipients converted

to sirolimus-based calcineurin inhibitor-free immunotherapy: 24-month results from the CONVERT trial. *Transplantation* 2011;92(3):303-10.

279. Mathew T, Kreis H and Friend P. Two-year incidence of malignancy in sirolimus-treated renal transplant recipients: results from five multicenter studies. *Clin Transplant* 2004;18(4):446-9.

280. de Fijter JW. Cancer and mTOR inhibitors in transplant recipients. *Transplantation* 2017;101(1):45-55.

281. Geissler EK, Schnitzbauer AA, Zulke C *et al.* Sirolimus use in liver transplant recipients with hepatocellular carcinoma: a randomized, multicenter, open-label phase 3 trial. *Transplantation* 2016;100(1):116-25.

282. Wilson RE, Hager EB, Hampers CL *et al.* Immunologic rejection of human cancer transplanted with a renal allograft. *N Engl J Med* 1968;278(9):479-83.

283. Florman S, Bowne W, Kim-Schluger L *et al.* Unresectable squamous cell carcinoma of donor origin treated with immunosuppression withdrawal and liver retransplantation. *Am J Transplant* 2004;4(2):278-82.

284. Loren AW, Desai S, Gorman RC *et al.* Retransplantation of a cardiac allograft inadvertently harvested from a donor with metastatic melanoma. *Transplantation* 2003;76(4):741-3.

Chapter 10. Risks related to the use of organs from donors with other conditions and diseases

10.1. Introduction

Besides infections (see Chapter 8) and malignancies (see Chapter 9), some pre-existing conditions and diseases in the donor can compromise organ function or can be transmitted by the organ to a transplant recipient. After donor evaluation and characterisation, a risk–benefit assessment for a particular recipient can be performed. This chapter provides general recommendations on the approach to follow when assessing donors with poisoning and donors diagnosed with different inherited diseases and other disorders. Reviewing the endless list of rare diseases in a single chapter is an impossible task. More than 3 500 rare diseases are described currently, and any rapid change in genetic research and analysis will change our knowledge about rare diseases. Therefore, it is recommended to consult specific up-to-date portals such as Orphanet (www.orpha.net). This French organisation has also translated guidelines into other international languages.

This portal includes a brief section about organ donation in the emergency guidelines adapted for some but not all rare diseases. Helpful contact details for experts and basic information can also be found at Orphanet.

10.2. Poisoning

There are more than 3 000 deaths by poisoning or intoxication per year reported in the United Kingdom. There is a large variation in rate and circumstances between countries, but most poisoning cases arrive in the hospital still alive and they represent a group of patients in whom organ donation should be considered [1]. An opioid epidemic is also a specific problem in the US. Published data are not sufficient to determine whether these deaths occur under circumstances that would easily allow diagnosis of brain death and the subsequent recovery of organs, and this is a major legal limitation, depending on the timing between poisoning, cerebral anoxia and death. Toxin uptake may occur by accident, through suicide or as a result of wilful poisoning by a third party. Established best practice is collaboration with legal investigating authorities (police, prosecution and forensics) in order to fulfil legal requirements and to await detoxification in order to perform proper brain-death diagnostics.

The number of cases where poisoning is the direct cause of brain death varies among registries, but the incidence is low. This rate is increasing in US, up to 6 % in 2014 [2] and 13 % in 2016 due to drug intoxication. Evolution to brain death mainly results from anoxia or brain oedema. Anoxic brain damage can occur as a result of a cardiac arrest due to myocardial ischaemia and fatal arrhythmias (e.g. cocaine) or a respiratory depression (e.g. barbiturates). Brain oedema might derive from an acute liver failure (e.g. paracetamol), hyponatremia (e.g. ecstasy) or unknown mechanisms (e.g. methanol). Haemorrhagic and ischaemic brain lesions are less frequent causes of brain death in intoxicated patients.

Table 10.1. **Reported cases of toxins and poisons leading to successful organ transplantation following brain death and considerations for assessment of the donor**

Substance	Heart	Lung	Liver	Pancreas	Kidney	Remarks
barbiturates	yes, careful assessment	yes	yes	yes	yes	
benzodiazepines	yes	yes	yes	yes	yes	
tricyclic antidepressants	yes, careful assessment	yes	yes	yes	yes	
neuroleptics	yes, careful assessment	yes, careful assessment	yes, careful assessment	yes, careful assessment	yes, careful assessment	Exclude multi-organ failure; wait for recovery from neuroleptic syndrome
cocaine	yes, careful assessment	yes	yes	yes	yes	Exclude multi-organ failure or sepsis; check for chronic abuse; check for elevated risk of HCV, HIV transmission; check for abuse of other substances Methadone can accumulate in the liver in long-term users
ecstasy	yes	yes	yes	yes	yes	
opioids	yes	yes, careful assessment	yes	yes	yes	
methadone	yes	yes	yes	yes	yes	
ethanol	yes	yes	yes	yes	yes	Chronic abuse: liver/pancreas damage
methanol	yes, careful assessment	yes	yes	yes, careful assessment	risk of rhabdomyolysis	Correct acidosis, wait until o.o mg/L
ethylene glycol	yes, careful assessment	yes	yes	yes	risk for oxalate	Correct acidosis
calcium inhibitors	yes, careful assessment	yes	yes	yes	risk of acute kidney injury	
venlafaxine	yes	yes	yes	yes	yes	wait for recovery from serotonin syndrome
acetylsalicylic acid	yes	yes	yes	yes	yes	
paracetamol	yes	yes	acute liver failure	yes	yes, careful assessment	
insulin	yes	yes	yes	yes	yes	
cyanide	yes	yes	yes	yes	yes	
colchicine	yes, careful assessment	ARDS: unsuitable	yes, careful assessment	yes, careful assessment	yes, careful assessment	Multi-organ failure
brodifacoum (rodenticide)	yes	yes	yes	yes	yes	
pesticide	yes, careful assessment	ARDS: unsuitable	yes, careful assessment	yes, careful assessment	yes, careful assessment	Multi-organ failure
malathion			yes		yes	
carbon monoxide	yes, careful assessment	yes	yes	yes	yes	

yes: donation of organ possible after proper assessment taking into account data from the literature.

yes, careful assessment: in these donors the poisoning might compromise the organ function irreversibly; otherwise the risk factors are listed in the table which may limit donation of a graft.

blank: currently no data available – donation can be considered after proper assessment.

ARDS: acute respiratory distress syndrome.

Opioids, carbon monoxide (CO), analgesics and antidepressants are the leading causes of fatal poisoning [3]. There is a great variety of reports on successful transplantation using multiple organs from brain-dead donors having suffered from various kinds of poisoning. However, there is no systematic

overview and it can be expected that only positive outcomes are being reported.

Hantson summarised case reports, expert opinions and other knowledge in this field exhaustively already in 1999, as did more recent reviews [4, 5]. In addition, there is one consensus document from the International Society for Heart and Lung Transplantation regarding drug toxicities and the use of cardiac allografts [6, 7]. The overall conclusions of these documents are as follows.

a. Patients who die due to or with intoxication by drugs or other substances should be considered as potential organ donors. Overdose-death donors (ODDs) have increased along with the worsening opioid epidemic. The risk of graft failure at 5 years is now considered similar for recipients of anoxic drug overdose donor grafts and recipients of other grafts [3]. Organs should be considered for transplantation following the routine biological and morphological assessment of the graft. Unless irreversible organ damage is confirmed, poisoning is not an absolute exclusion criterion for organ transplant. Heart transplantation outcomes in the UNOS database from donors dying of drug intoxication are similar to those from donors dying from other mechanisms [4].

b. Discussion with experts in toxicology or pharmacology is helpful or necessary to evaluate the suitability of different organs for transplant, but may be difficult in emergency or during the night. As these professionals may not be experts in the field of transplantation, case-by-case decisions have to be made collaboratively, taking into account the risk of organ dysfunction and the specific situation of a patient on the transplant waiting list. Collaborative experiences and cumulative data should be developed.

c. A list of websites and telephone numbers with 24 h services for intoxication advice should be available to donor co-ordinators locally.

d. The diagnosis of brain death may be complicated in cases where a given drug or poison has a direct or temporary influence on brain cells and their functioning (see Chapter 3). In addition, some sedative drugs used during intensive care management can also interfere with brain activity. Proper determination of brain death is still possible in poisoned patients when the injury responsible for irreversible brain damage has been identified (e.g. hypoxic brain damage in the case of opiate intoxication). Primary hypothermia due to secondary complications after poisoning must be corrected before undertaking brain death testing. Ancillary tests to prove the cessation of cerebral perfusion (e.g. transcranial Doppler sonography, cerebral angiography, cerebral perfusion scintigraphy or cerebral CT-angiography) are recommended. The reason is that some poisons interfere with the interpretation of certain electro-physiological tests (e.g. barbiturates can affect electro-encephalogram results). Usually, in patients admitted to an intensive care unit, most (or all) of the toxin can be eliminated before brain death diagnosis is initiated. Metabolites or delayed action should also be considered, and specific dosage or pharmacokinetics recommended. If complete detoxification cannot be confirmed or the toxin is still able to influence central nervous system cell function, then interference with electrophysiological measurements could be a major issue, whereas confirmed cessation of cerebral perfusion is a measurement independent of such interactions.

e. The risk of toxin transmission to a recipient can be further limited by continued detoxification during evaluation of organ function in the deceased donor.

f. In this context, information about the period of ingestion of drugs (either in chronic use or as single event) is valuable, in order to identify co-existing behavioural risk factors concerning the acquisition of a potentially transmissible infection (e.g. chronic intravenous drug abuse is associated with a higher probability for recent hepatitis C infection; see §8.2).

10.2.1. Basic considerations

Generally, organ donation is considered possible if there is no evidence of functional or structural damage of the organs in question. Organs from donors with poisoning that leads to brain death need to be evaluated according to case history and information about the specific toxin involved. The following points should be considered for potential donors with poisoning:

- Identification of agent(s) causing the poisoning. Multi-agent poisoning should not be overlooked.
- Acute poisoning should be differentiated from chronic poisoning or substance abuse with an acute overdose.
- The type and effectiveness of elimination therapy should be taken into account. Observation of the patient's medical status during this elimination period helps to exclude irre-

versible organ damage or risk of toxin transmission. Possible redistribution from fatty tissue and the extra-vascular space following clearance from the blood should not be overlooked. Experts in toxicology can provide data about tissue concentrations and elimination methods and times.

- Irreversible damage of specific organs should be excluded, and the extent of organ recovery after poisoning should be evaluated.
- Toxins not completely eliminated from specific organs may be transmitted to the recipient during transplantation with consequent adverse effects (e.g. solvents) or without any serious consequence (e.g. some narcotics). After a proper assessment of the preconditions for brain-death certification, which includes adequate detoxification, this risk can be assumed to be negligible.
- Appropriate recipients should be selected on the basis of acceptable risk levels.
- For the certification of death by neurologic criteria, intoxication by sedative or narcotic medications/substances must be ruled out and the cessation of cerebral circulation must be confirmed.
- In some poisoning cases, it may be impossible to identify the toxic agent because of inappropriate samples, rapid toxin elimination before sampling could take place or suitable measurement techniques not being available (e.g. blood or urine testing may be inconclusive for short-acting recreational designer drugs). In such cases, even though the process is time-consuming (days) or not available, as far as possible the most common toxic agents should be ruled out by chromatography screening. If any suspicions remain, organs should only be used at an increased risk level.
- Intoxication is not a natural cause of death. Therefore, any donation procedure should ensure that interference with criminal investigations is ruled out by proper prospective collaboration with the authorities performing forensic investigations.
- In cases of chronic substance abuse, consideration should be given to the risks discussed in Chapter 8 and Chapter 9.
- In cases where poisons were inhaled, acute or chronic lung injury must be properly assessed. Lungs without damage should be considered for transplantation.
- Organ viability must be checked against other existing pathologies and co-morbidities, especially after resuscitation events, extracorporeal membrane oxygenation (ECMO) support or hypoxia arising from the poisoning [2-9].

10.2.2. Poisoning agents

The following is a non-exhaustive list of toxic agents potentially causing brain death, and being the underlying cause of death of potential organ donors. The prevalence of toxic agents may vary between countries and over time [2].

a. *Amanita phalloides*
Liver donation is obviously not considered, as the liver is the direct target organ of poisoning by *Amanita phalloides* and other mushrooms. Acute renal failure is a frequent complication due to dehydration, but not directly due to the toxin. Other organs may be also considered for donation after normal routine biological and morphological assessment of the graft.

b. *Antidepressants/tricyclic antidepressants (TCA, e.g. amitryptyline)*
Fatalities after acute TCA overdose are becoming less frequent since the introduction of newer generation antidepressants, i.e. selective serotonin re-uptake inhibitors (SSRI). Death is mainly caused by fatal cardiac arrhythmias, shock or status epilepticus.
Hearts for donation should be evaluated critically, particularly in patients with abnormal electrocardiographic findings or high serum concentrations of TCA (> 2000 ng/mL). Liver, kidney or lung donation remains possible, based on the results of routine laboratory tests. The recommendation is to determine the concentration of TCA in the recipient, although there is no definite evidence in the literature of a significant risk of transmission to organ recipients.

c. *Chemical solvents*
This requires an individualised decision. Most solvents lead to cardiac arrest due to arrhythmias, and there is an endless range of such solvents. Adherence of solvents to lipids or their hydrophilic effects and the possibility of destruction of tissues and secondary lesions (e.g. accumulation of a substance in hepatic tissue, rupture of intestine leading to peritonitis) should be considered.

d. *Cocaine*
This narcotic causes early atherosclerotic lesions and also dilated cardiomyopathy in cases of chronic abuse. Atherosclerotic lesions are most likely to occur in the coronary arteries at an early stage. Therefore, special attention should be paid to atherosclerosis in potential heart donations after chronic cocaine use and a coronary angiography should be discussed. However, multivariate analysis revealed no difference in mortality or development of coronary artery disease at 1 and 5 years between transplant recipients who received an organ from donors with a history of cocaine use and transplant recipients who received an organ from donors having no history of cocaine use. A number of successful heart, lung, liver and kidney transplants have been reported, especially after acute poisoning associated with massive brain injury (e.g. haemorrhage). In cases where cocaine has been inhaled, acute or chronic lung injury must be properly assessed. Lungs without damage should be considered for transplant.
Cocaine abuse may be associated with an increased risk of viral infections in their window period (e.g. hepatitis C after intranasal cocaine sniffing). The metabolite coca-ethylene is formed after simultaneous consumption of cocaine and ethanol and is more cardiotoxic than isolated cocaine.
In contrast, no reports exist currently which have investigated the risks associated with cannabis abuse.

e. *Cyanides*
Cyanides are rapidly absorbed through the skin and can lead to irreversible inhibition of mitochondrial cytochrome oxidase. The toxicity of cyanides may be reversed rapidly by specific therapy (hydroxo-cobalamin). Following cardiac arrest, a few cases of successful heart transplantation after cyanide intoxication have been reported after resuscitation with hydroxocobalamin. Successful transplantation of all organs following cyanide intoxication in the donor is possible, provided that effective antidote therapy has been used and no more cyanide is detected in blood.

f. *Ethylene glycol (see also Methanol)*
Ethylene glycol (EG) is metabolised in the body by alcohol dehydrogenase into oxalic, glycolic and glyoxylic acids, leading to metabolic acidosis. Patients can be treated with ethanol or 4-methylpyrazole to inhibit the alcohol dehydrogenase, and sometimes with dialysis. Although the kidneys (the target organ for EG) may be damaged due to tubular necrosis or oxalate deposition, transplant may be considered after recovery from this complication. Heart, lung or liver donation may also be considered. EG poisoning may occur in combination with methanol.

g. *Ecstasy (3,4-methylenedioxymethamphetamine)*
This drug may cause brain death due to secondary complications after excessive use, but also after first time or single use. Successful organ transplants (heart, lung, kidney, pancreas, liver) of ecstasy-poisoned donors have been reported without detectable transmission of the agent to the recipient [5]. However, ecstasy can cause fulminant liver failure in some cases, with the urgent need for liver transplantation of the poisoned patient due to unknown or possibly an immune cause. In heart evaluation, ischaemia or myocardial necrosis should be ruled out, since these complications have been described in relation to coronary spasm and arrhythmias in patients intoxicated by 3,4-methylenedioxymethamphetamine.

h. *Ethanol*
All organs may be used, except for those confirmed with organ damage related to chronic abuse. Heavy alcohol consumption does not adversely affect heart transplantation, and there is no clear evidence of adverse outcomes after lung transplantation. There are no overall effects of cannabis or cocaine on survival after heart or lung transplantation [5].

i. *Insulin*
There is no contraindication to organ donation, but normalised electrolyte and glucose metabolism is preferred [2]. Monitoring of glucose and electrolytes is standard practice.

j. *Methanol (see also Ethylene glycol)*
Intoxication is not uncommon in countries where people produce their own alcoholic spirits without strict governmental controls. Cases have been reported where branded spirits and drinks have been diluted with methanol, causing intoxication. Methanol is rapidly absorbed by the gastro-intestinal tract and is metabolised by alcohol dehydrogenase into formic

acid, leading to metabolic acidosis. Patients can be treated with ethanol and 4-methylpyrazole to inhibit the alcohol dehydrogenase, and sometimes with dialysis.

Although the kidneys may be damaged as a consequence of shock and multi-organ failure (the kidney is not a target organ for methanol poisoning), there are a number of reports of the successful transplantation of all organs after fatal methanol intoxication, dependent on the serum methanol concentration remaining at organ procurement. Liver, heart, lung, kidney and, in some cases, pancreas transplantation might be possible if methanol remnants are absent from the serum and if metabolic acidosis is fully corrected.

k. *Opiates and methadone*
Except for the risk of temporary respiratory problems before terminal failure of the brain stem, no obstacles concerning organ donation exist. Caution is required because of the increased risk of acquired infections in the context of intravenous drug abuse or methadone substitution. Even though ODDs have higher rates of hepatitis C, cardiac allograft quality indices are favourable and recipient outcomes are similar when compared with non-ODDs. [5, 6]
With methadone, and particularly in patients on maintenance therapy for a long period with high dose, heart donation should be considered carefully. There is also a theoretical risk of accumulation of methadone in numerous tissues. The risk is minimal in patients with a single methadone overdose.

l. *Organophosphate pesticides*
This requires careful evaluation of the donor due to the risk of tissue accumulation and cardiac arrhythmias. It is important to identify the substance and to ensure that maximum terminal elimination half-life has been exceeded before organ recovery (e.g. parathion > 140 h) [8].

m. *Paracetamol*
In cases of acute liver failure due to paracetamol poisoning, irreversible liver injury may exist. However, in cases of brain death, all other organs may be recovered for transplantation. Acute kidney injury may occur, but is usually reversible.

n. *Rodenticides (dicoumarin) and other anticoagulants*
Coagulation disorders should be considered, due to ongoing vitamin K deficiencies until the recovery of the liver. The liver itself continues to function normally. Transplantation reports are lacking.

o. *Selective serotonin re-uptake inhibitors (SSRI)*
Fatalities following SSRI overdose appear less frequent than with TCA. Death is usually the consequence of brain failure (seizures) or sometimes of multiple organ failure in the event of a serotonin syndrome with high degree of hyperthermia. Organ removal should be possible, provided that the function of the organs is preserved. Cardiotoxicity is exceptional, but should be evaluated by routine testing (electrocardiogram, echocardiography and troponin).

p. *Other drugs or poisons*
In the event of intoxication or poisoning by unusual drugs or substances, a careful examination of the case has to be made jointly by the intensive care physician, the donor coordinator, a clinical toxicologist and the transplant team. This careful analysis and recording of the case could help decision making in future cases.

Reported cases of toxicity and poisonings leading to successful organ transplantation following brain death are summarised in Table 10.1 [1, 7-9].

10.2.3. Unusual conditions

The following unusual conditions or environmental hazards require consideration of the effect of multiple agents and or events:

a. *Burning and smoke inhalation*
In the worst cases, burn victims may have a combination of poisoning (smoke inhalation, carbon monoxide and cyanide). Proper treatment does not preclude organ donation in case of certified brain death.
Smoke is a mixture of CO, particulate matter and other gases, which may include cyanide. Detailed information is required about the circumstances of smoke inhalation. If cyanide and CO poisoning are treated properly, smoke inhalation should not prevent organ donation (see individual toxins). Bronchoscopy for bronchial examination and cleaning is

recommended. Lung transplantation has also in some cases been performed [10]. Renal toxicity has been debated regarding chronic use of surrogates for cigarettes [11].

b. *Carbon monoxide*
The literature dealing with CO poisoning mentions several cases of successful transplantation of heart, lung, kidney and liver obtained from CO-poisoned donors [12, 13]. Only 11 cases reporting on this topic have been published. Suitability for kidney transplant generally, such as creatinine, urine production and post-procurement biopsy, should be applied to CO-poisoned donors to assess whether or not ischaemic damage to the kidneys is recoverable. All organs procured from donors with carbon monoxide poisoning and burns survived during follow-up. As the brain and the heart appear particularly sensitive to hypoxia, a careful examination of cardiac function is mandatory before accepting heart donation. As a minimum, the following criteria have to be respected: no cardiac arrest or a very short period of cardiac arrest, rapid successful resuscitation and normal echocardiography.

c. *Drowning*
Drowning and asphyxia (A/D) are associated as one cascade: cardiac arrest and asphyxia after drowning are not *per se* a contraindication to organ procurement. When the possible donor has been stabilised at the ICU, the requirements for correct certification of death must be fulfilled. In donor and organ selection, the complications associated to asphyxia have to be evaluated. Recent studies suggest that results in lung transplantation with grafts procured from donors whose cause of death is A/D are equivalent to cases of other cause of death [14, 15]. The only issue here is careful evaluation of the organs including the question of tracheal airway exposure to fresh water or salt water and the contamination of the different pathogens in it including the risks of systematic spread [15] as well as exclusion of tissue damage.

10.3. Inherited or congenital diseases

Potential organ donors who have a genetic disorder or inherited disease may have suffered a lethal incident unconnected with their condition. In such cases, organ donation must be considered. However, some genetic disorders cause various enzyme deficiencies which are linked to different metabolic pathways in the liver. Some of these genetic disorders with enzyme defects can be fatal, since no alternative pathway exists for metabolism except for the one linked to the liver tissue, and therefore they may be a major cause for contraindicating liver transplantation. Detailed lists of inherited kidney and liver diseases are available in recent reviews and are very important in organ-specific selection criteria [16, 17]. Other gene defects may result in connective tissue disorders, haematopoietic disorders or predisposition for malignancies, or they may cause other terminal organ damage.

The basic considerations and strategies outlined below contribute to assessing organ donors diagnosed with inherited diseases. They may also be applied when assessing donors with non-inherited and other congenital diseases.

10.3.1. Basic considerations

Experience with the transplantation of organs recovered from donors with genetic disorders is limited. To date, a registry of donations associated with rare diseases has not been established, although this is an issue in about 1 % of all donation cases and, in each case, an individual decision pathway has to be followed. The definition of a rare disease is variable from one country to another but in Europe the definition is a prevalence of 1/2000. The diagnosis process may be long and not compatible with an emergency situation, including extensive clinical screening, family exam and finally, specific genetic tests. Those are increasingly used to characterise the (often private) causative mutation(s).

The European database Orphanet (www.orpha.net) provides regular updates of information about rare diseases. The section on emergency guidelines briefly mentions organ donation for each particular rare disease, but it remains a growing summary of guidelines for an endless list of rare diseases.[1]

Certain genetic diseases are more common in some regions in Europe. Experience in organ recovery exists for familial amyloid polyneuropathy (FAP), autosomal dominant polycystic kidney disease (ADPKD) and haemochromatosis. Sixteen cases of donor procurement from polycystic kidney disease were identified. Median donor age was 24. Kidneys from ADPKD donors could be offered, if they have

1 International case references can also be found at www.rarediseases.org/rare-disease-information/rare-diseases (Nord) or at http://ghr.nlm.nih.gov/BrowseConditions (Medline Plus).

had a full assessment, and could be considered acceptable for renal donation to recipients who may have a life expectancy of 10 years or less and who are fully informed [18].

In some cases, common knowledge should enable a decision to be made about using a graft in a particular recipient or not. For example, transplant of a liver from a donor with a congenital coagulation disorder related to a Factor V Leiden mutation, or a Protein S or C deficiency, will require anti-coagulation therapy in the graft recipient. *Post mortem* diagnosis and genetic analysis is not allowed by the law in many countries. Rapid development of genetic analysis (exome analysis) is now possible. It is frequently allowed during medically assisted procreation due to the benefit for the recipient and the consent for the donator. Indirect benefit could also be proposed to the family of the donor in case of discovery of an inherited disease. But this information could be addressed in its ethical aspect by a geneticist.

Sometimes it is impossible to detect latent genetic disorders or metabolic deficiencies, for example late-onset ornithine transcarbamylase (OTC) deficiency. Transplantation of an organ from a donor with an undetected genetic disorder risks impaired organ function or failure in the recipient with potentially severe consequences, and may require re-transplantation. In some heterozygous defects, the disease may only manifest in the recipient, for example Protein S deficiency [19]. Genetic disorders [19-22] should be considered when assessing donors with known thrombocytopenia, haemochromatosis, mitochondrial deficiency and/or mental disorders not related to infection, poisoning or malignancy. Another example is represented by APO L1 gene abnormality in some African-American populations, with consequences for the longevity of kidney transplant recipients exposed to the problem of risk assessment of the donor [20].

Some authors highlight the need to consider determination of plasma ammonia as part of the routine evaluation of all brain-dead donors. The isolated finding of hyperammonemia in a brain-dead person suggests a disorder of the urea cycle such as ornithine transcarbamylase deficiency [22]. Although this deficiency is a contraindication for liver donation, this does not extend to other organs such as kidneys, as these organs are not affected by the disease. Until not long ago, donors with a history of renal stones or with stones emerging during screening on imaging were not considered ideal, but recent guidelines have adopted less stringent criteria for potential donors at risk of stones [23].

In contrast to deceased donors for patients with selected, inherited, homozygote metabolic disorders requiring liver transplant, it is possible to use a living segmental-liver graft from a related heterozygote donor [20].

Whenever an inherited or congenital disease is suspected in a potential donor, the following steps should be followed to clarify the suitability of each organ or tissue for transplantation:

◊ Establish the diagnosis by collecting all available data and by consulting the experts responsible for the care of the donor. This may require specific sampling for examination by specialised centres (national reference centres).
◊ Each organ or tissue under consideration for procurement must be checked for its functionality and level of damage. Impaired or damaged organs should not be transplanted. In some cases, a different metabolic pathway exists that might resolve the problem; for example, in glycogenosis type 5 (McArdle disease), an enzyme defect affects all cells (especially muscle cells), but this defect is successfully mitigated in liver cells due to an enzyme coded on a different gene performing the metabolism.
◊ The risk that organs from donors with inherited diseases will transmit a genetic defect to recipients needs to be carefully considered. This assessment needs to be weighed against the possibility of post-transplant therapy in the recipient, and its associated risks, or the emergency needs of a recipient.
◊ All transplant teams involved must be aware that this assessment procedure is time-consuming and requires an inter-disciplinary approach.

For further information about diseases, contact with experts and emergency guidelines, see:

◊ www.orpha.net
◊ www.rarediseases.org
◊ http://ghr.nlm.nih.gov/BrowseConditions/.

10.3.2. Examples of inherited disorders in cases of organ donation

a. *Enzyme abnormalities and FAP*

A remarkable example of genetic disorders affecting the question of graft use is FAP [21]. In Portugal, Spain and Sweden, specific populations suffer from this disease at an exceptionally high prevalence. For some patients, liver transplant may be the only therapeutic option. FAP is characterised by the ongoing destruction of nerves (and other tissues), with an onset of sensory-motor polyneuropathy in the lower limbs. Due to a point mutation of the transthyretin or prealbumin gene, endoneurinal amyloid deposits occur that are responsible for irreversible damage by amyloid aggregates between the ages of 30 and 50 years, unless a functioning

enzyme pathway is introduced through a liver transplant. The otherwise healthy livers of FAP patients can then be used in non-FAP patients (or even divided among two recipients) waiting for liver transplant in a so-called domino liver transplantation procedure [24, 25]. However, FAP is, without exception, ultimately transmitted to these domino transplant recipients and clinically manifests after a variable time period. If risk–benefit could be considered in hepatocellular carcinoma, transmission of FAP could occur after a variable delay from 5 to 10 years.

On the other hand, serious adverse outcomes are described in cases of hyperoxaluria, acute intermittent porphyria, apolipoprotein A1 amyloidosis, lysozyme amyloidosis and acute intermittent porphyria.

b. *Autosomal dominant polycystic kidney disease*

ADPKD is not a contraindication to organ donation; even polycystic liver and kidneys can be considered for transplant. In the case of associated complications in other organs, for example polycystic liver disease, it is advisable to assess graft quality at recovery and to transplant into suitably selected recipients. Some gene carriers are at higher risk of developing subarachnoid bleeding after rupture of a cerebral aneurysm. The published literature is encouraging and supports the use of polycystic kidneys from younger deceased donors. Therefore, we believe that if kidneys from ADPKD donors are offered, they should have a full assessment and be considered acceptable for renal donation to recipients who may have a life expectancy of 10 years or less and who are fully informed and have the capacity to consent to receiving a polycystic kidney [18]. In contrast, in a young donor (e.g. < 30 years) with normal kidney function but having an enlarged kidney typical of ADPKD, deterioration of kidney function and other complications are likely to occur over an unpredictable time frame, thereby warranting a reluctance to use the kidneys.

There is no reported case of liver failure in patients with ADPKD. Some authors suggest that the selective use of polycystic donor livers containing small cysts with preserved liver function is safe. Cardiovascular abnormalities are the most important non-cystic manifestations of ADPKD. A careful clinical evaluation of cardiac function by routine testing is mandatory before heart donation for transplantation is considered.

c. *Congenital coagulation disorders*

Factor V Leiden mutation. Affected patients with recurrent thrombosis need anti-coagulation therapy, thereby exposing them to the risk of intracerebral bleeding. Organ donation is possible although, in the case of liver transplants, the defect will be transmitted and recipients will require anti-coagulation therapy, with a consequent high to unacceptable risk to the recipient's life.

Haemophilia. The type of haemophilia must be determined, which will indicate the location of the gene defect. If it is attributable to one organ, for example liver, the other organs can be used without elevated risk. However, transplantation of an affected organ transmits all the complications associated with the type of haemophilia to the recipient. Some authors suggest that haemophilia donors should not be precluded from organ donation. However, high levels of factor VIII inhibitor in the donor before organ procurement represent an absolute contraindication to liver donation [26].

d. *Trisomy*

There are several types of trisomy. If organ function *per se* is not affected, it can be used as a graft.

e. *Connective tissue defects (e.g. Marfan syndrome)*

Although organ functioning at the cellular level is good, transplant practitioners are reluctant to use organs or tissues (e.g. heart, heart valves, arteries) due to destruction of the vascular walls. Experts should be consulted before a final decision is made. There is a risk of transmitting the defect, but there are no data on whether or not vascular walls would undergo further destruction after transplantation.

f. *Phacomatosis and neurofibromatosis*

Four major types are described in this inherited condition that are genetically and clinically different. In the case of neurofibromatosis type 1 (Morbus Recklinghausen), organ donation is possible if the increased risk (5%) for development of other malignancies is properly considered (e.g. optic glioma, astrocytoma, phaeochromcytoma, GIST). Neurofibromatosis type 2 is related to bilateral Schwannoma (WHO°1) of the 8th cranial nerve. Irradiation

could increase the thrombotic risk in organs. Tuberous sclerosis (la sclérose de Bourneville) should be excluded.

Donors with von Hippel–Lindau syndrome could be considered (preferably for the lung, heart and liver donation) when the risks associated with renal cell carcinoma and other malignancies are excluded when using organs according to the guidance in Chapter 9.

g. *Further examples*

Table 10.2 provides a non-exhaustive overview of inherited, congenital or otherwise acquired diseases where organ donation has been realised with success, and other cases where transplantation of single organs did not have a successful outcome [26-32].

Table 10.2. **Examples of successful/unsuccessful donation in cases of inherited, congenital or acquired disease**

Disease	Organs	Comment
Rendu–Osler–Weber syndrome	kidney	Successful transplantation is reported [27]
HELLP syndrome	kidney	Successful transplantation is reported [28]
IgA-nephropathy	kidney	Depending on the degree of kidney damage the graft may be used, since immunosuppressive therapy may be therapy of original disease [29]
	other organs	Can be used for transplantation
Moyamoya disease	heart, kidney, liver, lung	After exclusion of defects in other organs due to vascular defects, transplantation is possible [30]
Gilbert syndrome	liver	Gene defect causes unconjugated hyperbilirubinaemia; impaired long-term outcome not observed [31]
Bleeding disorders	liver	In cases with isolated factor XII, VII, XI deficiency in short term, no adverse events are observed (haemophilia A should be excluded) [32]
	other organs	Can be used for transplantation
Thrombotic disorders	liver	In the case of a donor with unknown Protein C, Protein S or Factor V Leiden mutation deficiency, serious thrombotic events are observed if the graft is used In the case of a donor with known Protein C, Protein S or Factor V Leiden mutation deficiency, recipients must be selected carefully; they should be able and willing to receive adequate anti-coagulation therapy after transplantation, though still with increased risk of thrombotic events [18, 33]
	other organs	Can be used for transplantation
Hereditary haemochromatosis	liver	In the case of heterozygote recipient receiving a graft from heterozygote or homozygote donor, disease is manifested which requires treatment of iron overload (no data available on long-term success); transplantation from a donor with sickle cell disease has also been considered [34]
Ornithine Transcarbamylase Deficiency	liver	Fatal outcome in deceased donation
	other organs	Can be used for transplantation
Alpha-1-antitrypsin deficiency	liver	Very likely to develop cirrhosis or fibrosis after some time, in which case retransplantation will be necessary; no long-term follow-up data available

Table 10.3. **Autoimmune and systemic disease: factors to be considered for donor- or organ-specific evaluation and selection**

Autoimmune and systemic disease	Donor (global)	Organ-specific				
		H	Lu	Liv	K	Pa
Primary sclerosing cholangitis (PSC)	consider carcinoma of the bile ducts and/or complications due to inflammatory bowel disease	Ev	Ev	N	Ev	Ev
Endomyocardial fibrosis	yes	N	Ev	Ev	Ev	Ev
Idiopathic lung fibrosis	yes with evaluation	Ev	N	Ev	Ev	Ev
Autoimmune hepatitis	yes with evaluation	Ev	Ev	N	Ev	Ev
Cutaneous lupus erythematosus	yes	Y	Y	Y	Y	Y
Systemic lupus erythematosus	yes (50 % of renal disease) [44]	Ev	Y	Y	Ev	Y

Autoimmune and systemic disease	Donor (global)	Organ-specific				
Heubner–Herter disease or coeliac disease	yes	Y	Y	Y	Y	Y
Pemphigus	yes after evaluation (cortisone, malignancy)	Y	Y	Y	Y	Y
Purpura rheumatica (Henoch Schönlein purpura)	yes	Ev	Ev	Ev	Ev	N
Sclerodermia	depends on degree of systemic involvement	Ev	Ev	Y	Ev	Y
Severe antiphospholipid syndrome	exclude if severe (evaluate in mild case)	Ev	Ev	Ev	Ev	Ev
Crest syndrome	yes	Y	Ev	Y	Y	Y
Goodpasture syndrome	yes	Y	N	Y	N	N
Gougerot–Sjögren syndrome	exclude lymphoma	Y	Ev	Y	Y	Y
Familial Mediterranean fever	check amyloidosis (M694V mutations in the FMF) [45, 46]	Y	Ev	Y	Ev	Ev

Y: yes; N: no; Ev: evaluation and discussion with expert.

10.4. Autoimmune defects and reactions

It is well known that autoimmune diseases can be transmitted by haematopoietic cell transplantation from the donor to an unaffected recipient. But only exceptionally has the occurrence of *de novo* autoimmunity in solid organ transplantation been described as donor-derived. Typically, these autoimmune diseases occur in the context of liver transplantation from a donor with documented autoimmunity (e.g. immune haemolytic anaemia and autoimmune thrombocytopaenia) [32]. Thereby the aetiology of post-transplant autoimmunity can be explained by graft-*versus*-host response in most cases and only exceptionally by direct transfer of antibodies from the donor during transplantation. Fortunately, in most cases no side-effects will be observed, since immunosuppression is also part of the therapy of autoimmune diseases.

An example of such rare complication is immune-mediated haemolysis by donor passenger lymphocytes which can produce anti-erythrocyte antibodies after previous immunisation of the donor against other minor ABO antigens as well as when recipients receive a compatible but non-ABO-identical graft (e.g. graft O into recipient A or B) [35].

Organs from donors with autoimmune diseases can be transplanted when any relevant organ damage can be excluded. Damage must be considered individually for each organ, transient complications of post-transplant autoimmunity being rare, but awareness about organ damage, early identification and appropriate treatment are important in patients at risk. Risk–benefit analysis for the recipient could be evaluated with an expert in this field, literature being relevant in case reports only and collected by a rare disease organisation like Orphanet.

Since immunological response to infections may cause cross-reactivity to antigens in the body with autoimmune reactions, the risks of such infections should be considered in the case of autoimmune diseases known in the donor. Helpful information can be obtained from the emergency guidelines provided by www.orpha.net or by application of the algorithm provided in Table 6.3 (see Chapter 6, §6.1).

To summarise:

◊ In the case of autoimmune diseases in the donor, monitoring of the recipient is recommended.
◊ Organs from donors with autoimmune diseases can be used for transplantation after exclusion of end-stage organ damage and infections associated with treatment with immunosuppressive drugs for autoimmune disorders.
◊ The potential risks of effects of donor-derived passenger lymphocyte activity in the recipients do not preclude organ donation itself.
◊ In the case of donors with erythrocyte antibodies, prospective monitoring of the recipients contributes to early detection and appropriate treatment of mediated haemolysis.

10.5. Allergies

Passive transfer of type I hypersensitivity reaction from donor to recipient has been reported with liver, lung, intestinal, kidney and heart transplantation [36-41]. Recipients suffered allergic reactions to peanuts, or nuts generally, after having received an organ from donors who died as a result of an anaphylactic reaction to those ingredients or from donors with well known allergic reactions to them in their medical history. There was a systemic response in the liver recipient and 'respiratory distress' in lung recipients.

These responses can be explained either by degranulation of donor food-specific IgE-loaded mast cells bound to liver or lung tissue after allergen ex-

posure, or to passive transfer of IgE retained in the liver sinusoids and bound to mast cells later on with the same effect (both persisting for months). In addition, there may be transfer of specific IgE-producing B cells, allergen-specific Th2 lymphocytes, stem cells or dendritic cells inducing IgE production together with the graft, causing allergic reactions (persisting long-term) in the recipient.

The exact mechanism causing this transfer of anaphylactic reactions cannot yet be explained; neither is it known why this happens in some but not all recipients nor why it is more or less often observed in grafts hosting more 'immune-reactive donor cells' (e.g. lung, liver, intestine) than others (heart, kidney, pancreas). Until further evidence exists, it is imperative that autoimmune disorders and allergies (mainly to food allergens) are considered as part of the donor health assessment. Since a residual risk of transferring an anaphylactic reaction to the recipient exists, this information should be passed on to the recipient centre, especially in the case of liver, lung and probably intestinal transplantation.

Due to post-transplant immunosuppression, recipients may acquire *de novo* allergies which are related to the graft and to the kind of immunosuppression received, such as tacrolimus or cyclosporine, but not to the issue of passive transfer from donor to recipient via donor lymphocytes or mast cells contained in the graft. Some studies suggest that post-transplant immunosuppression with tacrolimus is linked to an increased occurrence of IgE-mediated sensitisation and manifestation of allergic disease. A risk of food allergy from 5 % up to 38 % in paediatric liver transplant recipients is reported [42, 43].

To summarise:

◊ In the case of known anaphylactic reactions in the donor history, this information must be included in the donor characterisation (section on autoimmune issues).

◊ Lung, liver and intestinal transplant recipients should be taught to avoid such allergen exposure (especially in cases of food allergies in a donor with known anaphylactic reactions).

10.6. Neurodegenerative diseases, demyelinating diseases

Neurodegenerative and demyelinating diseases are caused by multiple different agents (e.g. ageing, genetics, autoimmune reactions, infections, exposure to environmental agents or unknown factors). Multiple co-factors further complicate the individual progression of these diseases.

When genetic defects or metabolic disorders cause such diseases, then transmission risks are not associated with a particular organ, unless the defect also causes damage to this organ. Further information about organ involvement can be extracted from www.orpha.net and/or from consultation of national experts listed there. When autoimmune defects cause such neurodegenerative and demyelinating diseases, then the rare event of transfer of autoimmune reactivity cannot be definitively excluded.

A new protocol suggests that patients with amyotrophic lateral sclerosis (ALS) are a viable source of tissue for organ transplantation [47]. However, multiple lines of evidence suggest that many neurodegenerative diseases, including ALS, might progress due to transcellular propagation of protein aggregation among neurons. ALS patients' grafts may serve as the sole life-saving materials available, making moot a discussion of ALS transmission risk.

To summarise, in potential organ donors with a neurodegenerative or demyelinating disease, it is essential to ensure that the disease:

◊ is not caused by an infection (e.g. prion disease in relation to variant Creutzfeldt–Jakob disease, HIV-related neurocognitive impairment) that excludes organ donation (see Chapter 8);

◊ is not associated with infectious complications related to specific treatment of the disease (e.g. progressive multifocal leukoencephalopathy, caused by JC virus after treatment by natalizumab in multiple sclerosis) or with the further course of disease that excludes organ donation (see Chapter 8);

◊ is properly diagnosed.

10.7. Solid organ recipient becoming an organ donor

Organ donation from donors with a previous history of solid organ transplantation represents a rarity, and clinical evidence is scarce.

Although experience and acceptance is steadily increasing, organs from such donors have still to be considered as marginal. This cautious view is due to co-morbidities leading to the need for primary solid organ transplantation itself as well as the side-effects of immunosuppressive treatment, including an increased risk of malignancy, infectious diseases and nephrotoxic side-effects. Primary evaluation of donors with a previous history of organ transplantation does not differ from standard evaluation. However, although the evidence level is low, pretransplant biopsy to evaluate organ quality should be considered. This applies especially for possible kidney grafts with close attention to signs of chronic toxic damage.

Outcomes following organ transplantation from donors with a previous history of transplantation differ according to the time interval from previous transplant to becoming an organ donor, and according to the type of graft recipient.

As described by Lee *et al.* [48] in kidney transplant recipients, the time interval until becoming an organ donor tends to be longer (> 1 year) than non-kidney transplants, age is higher and the leading cause for death is a cerebrovascular event.

This timeline eventually differs from previous heart, lung or liver transplant recipients. These donors tend to be younger, and to survive a shorter period of time from transplant until becoming organ donors (weeks to month). In such donors cardiovascular events represent a primary cause of death.

10.7.1. Outcomes

The 5-year graft survival of both kidney and liver grafts from donors with a previous history of transplantation and a survival of more than one year has been shown to be significantly lower than the 5-year graft survival of 'conventional' grafts. However, multivariable analysis has demonstrated a comparable survival rate, if donor survival following transplantation was shorter than one year. In regard to cardiac and lung graft survival, 5-year graft survival did not differ from conventional cardiac or lung grafts. In regard to pancreas donation from donors with a previous history of transplantation, data are lacking.

In summary, due to the discrepancy between available organs and patients awaiting life-saving transplantation, acceptance of organs from donors with a previous history of transplantation is acceptable. However, clinical evidence is mostly based on single centre experience and/or case reports.

10.8. Conclusions

Multiple disorders or conditions exist that may be perceived as contraindications to organ donation due to potential additional risks to organ recipients. This chapter is not exhaustive in listing such disorders, but provides recommendations about the use of organs from donors with a variety of diseases and conditions. Before dismissing any potential donors, it is necessary to assess each case individually and, when literature or reference websites cannot provide all information needed, experts in the field should be contacted.

Research agenda

From the literature and discussion of the available evidence, several topics have been identified for which evidence is inconsistent, insufficient or non-existent. The authors of this guide recommend that future research should focus on the following research gaps:

1 Genetic testing of donors and recipients
2 Follow-up of recipients who received an organ from a donor with other risk conditions, as a way to better define the safety limits of organs from these donors.

10.9. References

1. Wood DM, Dargan PI, Jones AL. Poisoned patients as potential organ donors: postal survey of transplant centres and intensive care units. *Crit Care* 2003;7(2):147-54.
2. Wood DM, Chan WL, Dargan PI. Using drug-intoxicated deaths as potential organ donors: impression of attendees at the American College of Medical Toxicology 2014 annual scientific meeting. *J Med Toxicol* 2014;10(4):360-3.
3. Wanis KN, Madenci AL, Dokus MK *et al.* The effect of the opioid epidemic on donation after circulatory death transplantation outcomes. *Transplantation* 2019;103:973-9.
4. Warraich HJ, Lu D, Cobb S *et al.* Trends and outcomes of cardiac transplantation from donors dying of drug intoxication. *Am Heart J* 2018;199:92-6.
5. Caballero F, López-Navidad A, Coturruelo J *et al.* Ecstasy-induced brain death and acute hepatocellular failure: multiorgan donor and liver transplantation. *Transplantation* 2002;74(4):532-7.
6. MacGowan GA, Dark JH, Corris PA and Nair AR. Effects of drug abuse, smoking and alcohol on donor hearts and lungs. *Transplant International* 2019;32(10):1019-27.
7. Phillips KG, Ranganath NK, Malas J *et al.* Impact of the opioid epidemic on heart transplantation: donor characteristics and organ discard. *Ann Thorac Surg* 2019 Oct;108(4):1133-9.
8. Mariage JL, Galliant A, Hantson P. Organ donation following fatal organophosphate poisoning. *Transpl Int* 2012;25(6):e71-2.
9. Bronchard R, Durand L, Legeai C *et al.* Brain-dead donors on extracorporeal membrane oxygenation. *Crit Care Med* 2017;45(10):1734-41.
10. Stöehr I, Nagib R, Franke A *et al.* Bilateral lung transplantation from a donor with fume poisoning. *J Heart Lung Transplant* 2007 Feb;26(2):194-5.
11. Räsänen M, Helanterä I, Kalliomäki J *et al.* A case report of successful kidney donation after brain death

following nicotine intoxication. *Transplant Proc* 2017;49(1):229-31.

12. Busche MN, Knobloch K, Herold C *et al.* Solid organ procurement from donors with carbon monoxide poisoning and/or burn – a systematic review. *Burns* 2011;37(5):814-22.
13. Siskind E and Jonsson J. Successful kidney transplant from donor with carbon monoxide poisoning. *Transplantation* 2018;102(8):e365.
14. Pasupneti S, Patel K, Mooney JJ *et al.* Lung transplantation following death by drowning: a review of the current literature. *Clin Transplant* 2016;30(10):1195-7.
15. Whiston BA, Hertz MI, Kelly R *et al.* Use of the donor lung after asphyxiation or drowning: effect on lung transplant recipients. *Ann Thorac Surg* 2014;98(4):1145-51.
16. Joly D, Beroud C, Grunfeld JP. Rare inherited disorders with renal involvement – approach to the patient. *Kidney International* 2015;87(5):901-8.
17. Schielke A, Filomena C, Goumard C *et al.* Liver transplantation using grafts with rare metabolic disorders. *Dig Liver Dis* 2015;47(4):261-70.
18. Shamali A, Milsom-Mcquillan S, Gibbs P. Outcomes of renal transplant from donors with polycystic kidney disease. *Int J Surg* 2018;51:229-32.
19. Schuetze S, Linenberge M. Acquired protein S deficiency with multiple thrombotic complications after orthotopic liver transplant. *Transplantation* 1999;67(10):1366-9.
20. Freedman BI, Locke JE, Reeves-Daniel AM, Julian BA. Apolipoprotein L1 gene effects on kidney transplantation. *Semin Nephrol* 2017 Nov;37(6):530-37. https://doi.org/10.1016/j.
21. Carvalho A, Rocha A, Lobato L. Liver transplantation in transthyretin amyloidosis: issues and challenges. *Liver Transpl* 2015;21(3):282-92.
22. Caballero F, Ris J, Puig M *et al.* Brain-dead donors with ornithine transcarbamylase deficiency: a big learning opportunity in clinical evaluation. *Am J Transplant* 2017 Aug;17(8):2229. https://doi.org/10.1111/ajt.14367.
23. Gambaro G, Zaza G, Citterio F *et al.* Living kidney donation from people at risk of nephrolithiasis, with a focus on the genetic forms. *Urolithiasis* 2019 Feb;47(1):115-23. https://doi.org/10.1007/s00240-018-1092-4.
24. Adams D, Samuel D, Slama M. Traitement des neuropathies amyloïdes héréditaires [Treatment of familial amyloid polyneuropathy] (in French). *Presse Med* 2012 Sep:41(9):793-806.
25. Mnatsakanova D, Živković SA. Iatrogenic amyloid polyneuropathy after domino liver transplantation. *World J Hepatol* 2017 Jan 28;9(3):126-30.
26. Hisatake GM, Chen TW, Renz JF *et al.* Acquired hemophilia A after liver transplantation. *Liver Transpl* 2003;9(5):523-6.
27. Caballero F, Leal J, Puig M *et al.* Organ donation and Rendu-Osler-Weber syndrome. *Transplantation* 2013 Apr 15;95(7):e47-8.
28. Flynn MF, Power RE, Murphy DM *et al.* Successful transplantation of kidneys from a donor with HELLP syndrome. *Transpl Int* 2001;14(2):108-10.
29. Koselj M, Rott T, Vizjak A *et al.* IgA nephropathy as a donor transmitted disease in renal transplant recipients. *Transplant Proc* 1991 Oct;23(5):2643-6.
30. Diaz-Guzman E, Neltner JM, Hoopes CW. Organ donation and Moyamoya disease. *Am J Transplant* 2012 May;12(5):1353-5.
31. Kaneko J, Sugawara Y, Maruo Y *et al.* Liver transplantation using donors with Gilbert syndrome. *Transplantation* 2006 Jul 27;82(2):282-5.
32. Friend PJ, McCarthy LJ, Filo RS *et al.* Transmission of idiopathic (autoimmune) thrombocytopenic purpura by liver transplantation. *N Engl J Med* 1990 Sep 20;323(12):807-11.
33. Haldar D, Chen F, Byron J *et al.* Is it time to revisit contraindications to organ donation from donors with a JAK-2 mutation? Safe use of a liver allograft from a donor with essential thrombocythaemia. *Transpl Int* 2015 Jul;28(7):881-3.
34. Rossidis A, Lim MA, Palmer M *et al.* Kidney transplantation from a donor with sickle cell disease. *Am J Transplant* 2017 Feb;17(2):569-71.
35. Nadarajah L, Ashman N, Thuraisingham R *et al.* Literature review of passenger lymphocyte following renal transplantation and two case reports. *Am J Transplant* 2013 Jun;13(6):1594-1600.
36. Chehade M, Nowak-Wegrzyn A, Kaufman SS *et al. De novo* food allergy after intestinal transplantation; a report of three cases. *J Pediatr Gastroneterol Nutr* 2004 May;38(5):545-7.
37. Legendre C, Caillat-Zucman S, Samuel D *et al.* Transfer of symptomatic peanut allergy to the recipient of a combined liver-and-kidney transplant. *N Engl J Med* 1997 Sep 18;337(12):822-4.
38. Phan TG, Strasser SI, Koorey D *et al.* Passive transfer of nut allergy after liver transplantation. *Arch Intern Med* 2003 Jan 27;163(2):237-9.
39. Khalid I, Zoratti E, Stagner L *et al.* Transfer of peanut allergy from the donor to a lung transplant recipient. *J Heart Lung Transplant* 2008 Oct;27(10):1162-4.
40. Boyle RJ, Hardikar W, Tang MLK. The development of food allergy after liver transplantation. *Liver Transpl* 2005 Mar;11(3):326-30.
41. Dewachter P, Vézinet C, Nicaise-Roland P *et al.* Passive transient transfer of peanuts allergy by liver transplantation. *Am J Transplant* 2011 Jul;11(7):1531-4.
42. Newman EN, Firszt R. Post-transplantation

development of food allergies. *Curr Allergy Asthma Rep* 2018 Jan 29;18(1):4.

43. Needham JM, Nicholas SK, Davis CM. Food allergies developing after solid organ transplant. *Pediatr Transplant* 2015 Dec;19(8):827-35.
44. Magoon S, Zhou E, Pullman J *et al.* Successful transplantation of a donor kidney with diffuse proliferative lupus nephritis and crescents – a case report. *Nephrol Dial Transplant* 2010 Dec;25(12):4109-13.
45. Yazawa M, Tsujita M, Goto N *et al.* Familial Mediterranean fever developing in a Japanese kidney transplant recipient. *CEN Case Rep* 2016 May;5(1):43-7.
46. Altindal M, Turkmen E, Yildirim T *et al.* Kidney transplantation for end-stage renal disease secondary to familial Mediterranean fever. *Clin Transplant* 2016 Jul;30(7):787-90.
47. Holmes BB, BA Diamond MI.. Amyotrophic lateral sclerosis and organ donation: is there risk of disease transmission? *Ann Neurol* 2012 Dec;72(6):832-6.
48. Lee GS, Goldberg DS, Levine MH, Abt PL. Outcomes of organ transplants when the donor is a prior recipient. *Am J Transplant* 2018 Feb;18(2):492-503.

Related material

Reporting form for rare diseases and intoxication (France, English-language version)

Chapter 11. Organ procurement, preservation and transport

11.1. Introduction

Organ procurement is a fundamental part of the transplant process. The success of any transplant procedure relies on a careful evaluation of the donor information, a well-conducted surgical procedure that ensures the removal of organs in perfect condition and an in-depth assessment of the donated organs.

Although the principles of organ procurement are always the same, there is variation in clinical practice and terminology (procurement, retrieval or recovery). We regard 'organ harvesting' as an inappropriate term that does not reflect the gift of life and has unwanted connotations in the public view. For the purpose of this chapter we used the term 'procurement', although 'retrieval' and 'recovery' are also acceptable.

11.2. Organ procurement team structure and logistics

It is a prerequisite that the retrieval team is fully conversant with the legal setting applicable to the country in which the retrieval is about to take place.

The structure of the retrieval team may include:

- Lead surgeon (s), fully trained in all aspects of abdominal and/or thoracic retrieval
- Assistant surgeon
- Theatre nurse
- Theatre practitioner (responsible for organ perfusion)

Once a donor has been identified, the donor co-ordinator should liaise with the retrieval team's co-ordinator to mobilise the team. In many situations the abdominal multi-organ team is attached to a liver transplant centre, and therefore the logistics of team mobilisation are handled by a co-ordinator. The local co-ordinator is responsible for:

- Arranging transport to and from the donor hospital
- Relaying donor details to the retrieving team
- Informing all team members of departure time, transport modality, destination and type of retrieval.

Organ procurement travel is associated with significant risks [1]. It is therefore the responsibility of the local team and the national transplant organisations to ensure that safe and standardised travel arrangements (by road or by air) as well as adequate standards for life insurance for the retrieval personnel are in place [2]. Best travel and insurance practices should be in place for the retrieval team, given the high risk of organ procurement travel.

11.3. Pre-retrieval checks

On arrival at the donor hospital, the team should go directly to the operating theatre, introduce themselves to the local team and familiarise with the theatre setup. The team should be aware that they act as ambassadors for transplantation and should act accordingly in the donor hospital.

The lead surgeon(s) should liaise with the donor

co-ordinator and ensure that all the necessary paperwork and relevant donor data are available for review. This should form part of the surgical safety checklist, where all the information pertaining to the donor, consent and organs to be retrieved are reviewed, prior to starting the procedure. This includes:

- Donor case notes for relevant history
- Brain death tests documentation (if applicable)
- Consent for donation and for specific organs to be retrieved
- Blood group (there must be clear documentation)
- Donor data, including haematology and biochemistry tests, microbiological results, and the amount of inotropic and ventilatory support, blood gases and chest x-ray (for cardiothoracic organs).

The donor's notes should be carefully reviewed for the relevant history and to confirm the accuracy of the data on the donor characterisation forms.

Once the pre-operative checks are completed, the lead surgeon should organise a short team brief and discuss the operative approach and the role for each team member.

If a thoracic team is present, a common approach (in particular with regard to the sequence of incisions, vena cava drainage and sequence of organ removal) is agreed to ensure a smooth process once the retrieval is under way. If heart retrieval following donation after circulatory death (DCD) is relevant, the additional steps should be emphasised during team briefing.

When the donor comes to theatre, the donor surgeon must check the identity of the donor.

The donor management should follow the established protocols for donor management in each country. In some countries such as Spain, once death determined by neurologic criteria – that is, brain death (BD) – has been declared, the donor co-ordinator takes care of the donor's treatment in the intensive care unit (ICU), and this bedside management continues in the operating room where the anaesthetist should ensure an adequate protective ventilatory strategy, optimal fluid balance or use of vasopressors guided by advance cardiac monitoring.

There is a lack of evidence for the use of antibiotic therapy specifically for the purpose of organ donation; the benefit should be carefully considered and it may vary according to the organ to be transplanted (see Appendix 19).

Prolonged hypotension is detrimental to organ quality (when this occurs during procurement). Should this occur, the team must be prepared to proceed with a rapid retrieval (cannulation and cold perfusion) to ensure successful retrieval of all intended organs.

The lead donor surgeon is also responsible for communicating all relevant findings to all surgeons who have accepted the organs for transplantation, with written documentation accompanying each organ and verbal notification of any anomalies or suspicious lesions.

11.4. Procurement

11.4.1. Donation after brain death

11.4.1.1. *Technical variations*

Several techniques for organ retrieval have been described. Although the principles are similar, there are a few notable differences.

11.4.1.1.1. Warm *versus* cold dissection

A retrieval procedure involves two phases: abdominal and thoracic organ dissection before aortic cannulation (warm phase) and further dissection and organ removal post-circulatory arrest and cold perfusion (cold phase). In the early years of transplantation, dissection and identification of the anatomy in the warm phase was the norm. Despite a more tedious dissection process [3], this allowed for a shorter cold phase, potentially reducing the risk of organ re-warming. However, damage of the arterial supply or vasospasm during warm phase dissection could compromise the organs and potentially render them non-transplantable.

The introduction of a rapid technique (*in situ* perfusion followed by cold phase dissection) [4] led to faster retrieval times and appeared to be associated with a lower incidence of organ damage and better organ function. However, correct identification of vascular anatomy in cold phase requires a higher level of experience. Prolonged dissection in the cold phase has been shown to be detrimental to both livers and kidneys. The retrieval surgeon should strive for an operative approach that balances rapid retrieval with their level of expertise and their ability to deal with these critical complications.

11.4.1.1.2. Single *versus* dual perfusion

There is a reasonable amount of evidence indicating that in the setting of multi-organ donation after brain death (DBD) retrieval, aortic-only perfusion provides a comparable if not better outcome for the liver graft [5], with significant advantages for the quality of the pancreas [6] and intestinal grafts, when

compared with dual aortic and portal perfusion. However, dual perfusion remains the standard in the setting of DCD donors, in order to provide a rapid cooling of the liver and minimise the risk of primary non-function.

11.4.1.1.3. *In situ versus ex situ* liver split

The liver can be split *in situ* or *ex situ*. Each technique has its pros and cons, and a uniform approach is yet to be established. There have been concerns regarding the quality of other organs retrieved when an *in situ* split is performed. However, data from centres that practise this approach routinely have failed to demonstrate an inferior outcome [7]. Irrespective of the approach, the splitting of suitable livers should be strongly encouraged.

11.4.1.1.4. Separate *versus en bloc* liver–pancreas removal

Traditionally, organs are removed individually in a certain order (thoracic organs, liver, pancreas, kidneys). A prolonged time to remove the organs after cold perfusion increases the risk of rewarming [8] and could lead to organ dysfunction post-transplantation. Furthermore, there is evidence that organ temperature does not drop as rapidly as previously thought, despite intravascular as well as topical cooling. Therefore, an *en bloc* technique has been advocated. This reduces the dissection and removal time, is associated with fewer procurement-related injuries and may be associated with better initial organ function [9]. There is no evidence to support a belief that either approach is associated with better outcomes (Appendix 20).

11.4.1.2. *Technique*

Irrespective of these differences, the technique employed must ensure a rapid and successful removal of organs with a minimal risk of damage. Most abdominal multi-organ retrievals include liver, pancreas and kidneys. The retrieval technique presented here is one of the many options available for this setting. Paediatric retrievals and multivisceral retrieval including small bowel are less common and should be performed by the recipient centre team, unless the retrieval team is familiar with these procedures.

Once the pre-operative checks are completed, the operating field is prepared and draped from the suprasternal notch to the pubis. A midline incision from the xiphisternum to the pubic symphysis is then made. The falciform and the round ligaments are divided, an abdominal retractor is placed and a thorough laparotomy is performed to identify any pathology. Once the laparotomy is completed, the falciform ligament is fully divided and a muslin pack is placed over the liver to protect it during sternotomy.

The suprasternal ligament is incised, taking care to avoid the suprasternal veins. Using blunt finger dissection and a combined suprasternal and infrasternal approach, a tunnel is created immediately behind the sternum, in the anterior mediastinum. A median sternotomy is undertaken, making sure that the ventilator is disconnected prior to sternotomy, to allow the collapse of the lungs and avoid any potential iatrogenic injuries. Once the sternotomy is completed, the ventilator is reconnected and lungs are re-inflated. Once the sternotomy is completed, the pleural edges should be gently mobilised using blunt dissection, to allow the placement of a Finochietto retractor. Haemostasis from the sternal edges is achieved using bone wax and diathermy.

A Finochietto retractor is placed in the wound and gradually opened. The pleurae are opened and the lungs are exposed. The pericardium is opened using scissors rather than diathermy and the heart is protected with a moist swab. The anterior aspect of the diaphragm can be incised to facilitate further opening of the retractor.

11.4.1.2.1. Visceral mobilisation and vascular exposure

A swab is placed under the left lateral segment of the liver to protect the viscera, and the left triangular ligament is divided close to the liver with care to avoid damaging the left hepatic and phrenic veins. The liver can now be fully inspected for the presence of aberrant anatomy [10], palpating the right side of the hepato-duodenal ligament for the presence of an aberrant right hepatic artery and lifting the left lateral segment to inspect the lesser sac for the presence of an aberrant left hepatic artery. The lesser sac is opened, preserving any aberrant artery.

The entire small bowel and the caecum are retracted by the assistant in a cephalad direction. This allows exposure of the white line of Told, which marks the correct plane of dissection. In obese patients this line of dissection may be harder to find but time should be taken to identify the correct plane as this facilitates exposure of the great vessels.

The colon and small bowel are mobilised, taking care to avoid damaging the right ureter and gonadal vessels. This right medial visceral rotation (Cattel–Braasch manoeuvre) exposes the inferior vena cava (IVC), aorta, right kidney and ureter as well as the left renal vein. The viscera are mobilised until the origin of the superior mesenteric artery (SMA) can be iden-

tified by palpation (immediately cranial to where the left renal vein crosses the aorta).

The SMA can be dissected and encircled at the level of its aortic origin. This is a useful manoeuvre, particularly if an aberrant right hepatic artery is identified during the latter stages of the dissection. This will facilitate and guide the vascular division in the cold phase. The SMA is surrounded by a fair amount of lymphatic tissue, which must be divided so the artery can be carefully identified and encircled.

At this point, it is useful to divide the peritoneal attachments to the inferior aspect of the right lobe of the liver, to prevent any capsular tears due to excessive traction by an over-zealous assistant.

The peri-aortic lymphatic tissue is divided, and the aorta and the common iliac arteries are exposed. The distal aorta is dissected circumferentially above the level of the bifurcation, taking care to avoid damaging the lumbar arteries. Two heavy ties/tapes are placed loosely around the aorta.

If a lower polar kidney artery arises from the distal aorta or the common iliac artery, cannulation can be undertaken via the contralateral common iliac artery, which is isolated at this stage.

Venous venting can be undertaken in the chest, as it does not compromise thoracic organ retrieval. However, the abdominal IVC can also be used for venting, and in this case, it should be dissected and controlled above the iliac bifurcation, in a similar manner to the aorta.

11.4.1.2.2. *Porta hepatis* dissection

The liver is retracted and the hepato-duodenal ligament is exposed. The peritoneum is incised about 0.5 cm above the upper border of the duodenum, and dissection is carried in a transverse manner from lateral to medial. Multiple small veins are encountered at this level and should be ligated and divided.

The common bile duct is encircled, ligated and divided above the duodenum. The gallbladder is opened and flushed with preservation solution until the effluent from the divided end of the common bile duct is clear. Bile is toxic and should be washed away assiduously.

In some European centres, the cystic duct is ligated either in the warm phase or in the cold/backtable phase, close to the infundibulum in order to exclude bile flow from the gallbladder. If this approach is adopted, integrity of the hilar structures must be checked and ensured.

Once the bile duct is divided, dissection in the *porta hepatis* is resumed from the medial side identifying the common hepatic artery. Dissection is then carried towards the right to identify the gastro-duodenal artery (GDA). The GDA is dissected towards the pancreas. A 5 mm stump of GDA must be preserved on the hepatic artery to allow for reconstruction options in case aberrant vasculature is present.

The common hepatic artery is then dissected towards the coeliac axis, staying above the upper border of the pancreas, which is gently retracted by the assistant. The origin of the splenic artery is identified and dissected for 5 mm, without straying into the pancreas and preserving any dorsal pancreatic artery, which occasionally may arise at this level.

The presence of aberrant hepatic vasculature must be ascertained during *porta hepatis* dissection. Several variations have been described. An aberrant right hepatic artery will be encountered on the postero-lateral aspect of the portal vein. The presence of a completely replaced hepatic artery from the SMA should be suspected if the portal vein (rather than the CHA and/or GDA) is encountered first during the dissection of the *porta hepatis* following the bile duct division. The presence of an accessory/replaced left hepatic artery should have already been determined when the lesser sac was opened.

11.4.1.2.3. Pancreas dissection

The lesser sac is entered dividing the gastro-epiploic vessels. The gastric antrum is isolated, and a vessel loop can be placed around it to mark the site of proximal gastro-intestinal tract transection for removal of the pancreas.

The greater curvature of the stomach is mobilised for a suitable length to facilitate a detailed inspection and palpation of the entire pancreatic gland. The proximal jejunum is then inspected and a vascular loop can be placed to mark the distal site of transection.

The descending colon is mobilised along the Told line, to expose the left kidney and allow placement of ice for topical cooling.

11.4.1.2.4. Supra-coeliac aorta preparation

The left lateral segment is retracted laterally and the supra-coeliac aorta is palpated through the lesser sac. The diaphragmatic crura are incised vertically over the aorta, using diathermy. Using forceps the divided crura are retracted and the aorta is dissected for a suitable length to allow placement of a clamp. There is no need to dissect the aorta circumferentially, but the dissection of the lateral aortic walls should be taken all the way to the spine to allow accurate clamping.

11.4.1.2.5. Vascular cannulation and cross-clamping

Having completed all these steps, after discussion with the cardio-thoracic team, 30 000 IU of heparin (300 IU/kg) are administered intravenously. After 5 mins, the small bowel is retracted cephalad and the distal aorta is exposed. The previously placed distal umbilical tape is ligated at the level of the aortic bifurcation.

The proximal tape is lifted to allow the surgeon to pinch and control the aorta. This manoeuvre must be gentle, particularly when aorta is atheromatous. A small incision is made and an appropriately sized cannula (usually a 22 Fr) is inserted in the aorta. The cannula should be primed and bubbles removed from the circuit prior to insertion.

The surgeon holds the aorta and the cannula to prevent displacement and significant blood loss, whilst the assistant secures the cannula in place tying the tape. The proximal end of the cannula should be 2-3 cm above the arteriotomy, and the surgeon must ensure that the tip is well below the origin of the renal arteries. Once the adequate position of the cannula tip is confirmed, the tape is looped and tied around the cannula again, to prevent inadvertent displacement.

Although aortic perfusion alone is the current standard for multi-organ DBD donors, portal perfusion may be used for marginal liver donors or if the liver is considered for *ex situ* split.

Portal vein cannulation can be achieved via several approaches:

- IMV cannulation
  The transverse colon is lifted and the inferior mesenteric vein (IMV) is exposed to the left of ligament of Treitz. The peritoneum is incised and the vein is dissected for a few cm. Cannulation at this level, however, could be difficult, given the size of the vein. Furthermore, the cannula can inadvertently be positioned in the splenic vein. Therefore the cannula should be manipulated until the position of the tip is confirmed in the portal vein at the level of *porta hepatis*.
  Note: The IMV should not be used when the pancreas is being retrieved, since the cannula causes back pressure on the splenic vein and pancreatic oedema.
- SMV cannulation
  The transverse colon is lifted whilst the small bowel mesentery is pulled down. The peritoneum over the junction between the transverse mesocolon and small bowel mesentery is incised. The SMA is palpated and the superior mesenteric vein (SMV) is dissected to the right of the artery. This approach could be difficult if there is a large amount of mesenteric fat.
  Note: Perfusion through the SMV creates high splenic vein pressure and oedema of the pancreas; it should not be used when the pancreas is being retrieved.
- Portal vein cannulation
  This approach is superior to the other two methods and must be used if the pancreas is being retrieved for transplantation as it avoids pancreatic congestion. The portal vein is identified in the *porta hepatis* and is dissected circumferentially approximately 1 cm above the upper border of the duodenum. A tie is placed around the vein and secures the cannula that is inserted towards the liver. As soon as perfusion is started, the portal vein must be completely divided, to allow unrestricted venous outflow from the pancreas and to avoid venous congestion.

Once the aortic cannulation is completed, the abdominal viscera are returned to the anatomical position to avoid arterial occlusion or spasm and to ensure uniform cold perfusion. Therefore, if vascular loops have been placed around the GDA and splenic arteries, ensure they are loose and not compromising the flow.

After consultation with the cardiac team, the cross-clamp time is agreed.

The left lateral segment is retracted to the right with the left hand and a long vascular clamp is positioned around the previously dissected supra-coeliac aorta, with the tip against the spine, to provide complete aortic occlusion.

The aorta is cross-clamped and the time is noted. The supracoeliac aorta should be clamped even if the cardiac team clamp the thoracic aorta. The heart is lifted and the cavo-atrial junction is incised sharply and exsanguination commenced. At the same time aortic perfusion is commenced.

Slush ice is placed around the liver, in the lesser sac on top of the pancreas, around the kidneys and around the mesenteric root. A sucker is placed at the level of supra-hepatic vena cava to keep the thoracic field clean. Some slush ice should also be placed in the right chest, above the diaphragm, to ensure uniform cooling of the liver and to avoid re-warming due to the blood draining in the right chest.

The organs must be constantly assessed and the caval effluent examined to ensure adequate perfusion. The operating theatre practitioner must inform the surgeons if there are any problems with the perfusion circuit and the flow. If problems are detected, inspect the aorta and ensure that the cannula is in the correct

position and not tied too tightly, and that there are no kinks in the circuit.

11.4.1.2.6. Cold phase dissection

Once the thoracic organs are removed, the abdominal organs are recovered either separately or *en bloc* (liver–pancreas).

11.4.1.2.7. *En bloc* liver–pancreas removal

The best way to remove the liver and the pancreas is *en bloc*. While waiting for the thoracic team to complete their part of the retrieval, the gastric antrum and the jejunum are divided with a linear stapler at the previously marked sites.

Once thoracic organs are removed, the stomach is fully mobilised along the lesser and greater curvature and the short gastric vessels are divided. The fully dissected stomach is then retracted into the chest to expose the pancreas and the supracoeliac aorta.

The transverse colon and the splenic flexure mobilisation is then completed and, when the aortic perfusion is near the end, the small bowel mesentery is stapled. The staple line must be well clear of the uncinate process to avoid damaging the pancreas and its blood supply. The small bowel and the colon are then retracted towards the patient's left iliac fossa. This exposes the entire retroperitoneum. The IVC is dissected and divided above the origin of the renal veins.

At this point, the left renal vein is divided flush with the IVC (although traditionally a small cuff is taken with the vein) and dissected to the left side of the aorta, to avoid injuries when the aorta is divided.

The aortic cannula is removed and the anterior wall of the aorta is incised up to the origin of the SMA (which was identified +/– slung during the warm phase dissection).

Once the renal arteries have been identified, an oblique incision is made towards the posterior aortic wall, to include the SMA on the aortic patch and separate it from the renal arteries.

At this point, the tail of the pancreas is mobilised, using the spleen as a handle. The lieno-renal ligament is divided, and dissection is carried out approximately 1 cm away from the upper and inferior borders of the pancreas to avoid capsular of vascular injuries. The left adrenal gland may be encountered, and in thin patients the kidney can be injured if dissection is not carried out under vision at all times.

The pancreas is mobilised until the left lateral aspect of the aorta and the level of aortic transection for SMA / renal arteries separation is identified. The posterior wall of the aorta is then dissected in a cephalad direction.

At this point, the inferior aspect of the liver–pancreas bloc is completely separated and attention is turned towards the supracoeliac dissection. The left diaphragm is divided to facilitate access to the aorta, which is divided below the previously placed cross clamp. The dissection of the posterior wall of the aorta is then completed, creating an aortic tube with the coeliac axis and SMA.

The suprahepatic IVC is completely divided and the surgeon should place a finger in the suprahepatic IVC to guide the next steps of the dissection.

The diaphragmatic dissection is carried towards the right, at the back of the IVC. The assistant retracts the liver to facilitate the division of the right diaphragm. Gentle traction is required at this stage to avoid capsular damage.

The right lobe is then separated from the right kidney (which is retracted downwards by the assistant), the optimal dissection plane being through the adrenal gland.

The liver–pancreas bloc is removed, dividing any remaining posterior attachments, and is placed in ice-cold saline solution on the bench.

11.4.1.2.8. Separate liver and pancreas retrieval

The liver and the pancreas can also be removed separately. In this case, the first step of dissection is the *in situ* separation of the liver from the pancreas. The GDA and splenic arteries have been identified (+/– looped) during the warm phase dissection. The assistant retracts the liver to expose the *porta hepatis*, and the GDA is divided, leaving a 5 mm stump on the hepatic artery. The pancreatic side of the GDA is marked with a fine suture and left open. The portal vein is now exposed and is divided about 10 mm above the upper border of the duodenum, marking the pancreatic end of the vein. The tissue behind the portal vein is carefully dissected to exclude the presence of an aberrant right hepatic artery.

The common hepatic artery is dissected towards the coeliac axis and the splenic artery is divided leaving a similar length with the hepatic artery, whilst the pancreatic end is marked for easier identification during bench surgery.

The left gastric artery is divided, or dissected from the lesser curvature of the stomach in the presence of an aberrant left hepatic artery.

The dissection is then carried out vertically down towards the aorta, on the left side of the coeliac axis. There is a large amount of lymphatic tissue, which must be divided to expose the coeliac origin. An aortic patch is created, taking care to avoid the SMA, which sometimes arises quite close to the coeliac axis origin.

In most cases, an aberrant right hepatic artery

(ARHA) arises from the SMA, close to its aortic origin, and can be identified in the warm phase, particularly if the SMA is dissected and placed on a loop. In this case, the SMA should be divided above the ARHA origin towards the pancreas, allowing an aortic patch with the SMA and the coeliac axis for the liver graft. An approach for dealing with aberrant hepatic arteries is presented in Chapter 7 (see §7.2.2*e*, §7.2.3*f*).

The diaphragm and the suprahepatic IVC are divided, and the liver is mobilised as previously described. At this point, the infrahepatic IVC is divided. The liver is removed, having divided the posterior retroperitoneal attachments.

The pancreas is removed next, following the steps described above. The gastric antrum, jejunum and small bowel mesentery are stapled. The aorta is divided above the renal arteries and the tail of the pancreas is mobilised medially. With a finger in the aorta and the tail rotated medially, the posterior wall of the aorta is dissected, dividing the remaining retroperitoneal attachments. The pancreas is then transferred to bench in cold saline solution.

11.4.1.2.9. Kidney removal

Kidneys can be removed separately or *en bloc*.

Having removed the liver–pancreas bloc, the aorta is divided above the distal tie and the posterior wall is incised between the lumbar arteries. Care must be taken during this step, to avoid damaging a potential retro-aortic left renal vein, and also to note any aberrant lower pole renal artery arising from the common iliac artery. The vascular pedicles of the two kidneys are now completely separated.

The posterior aspect of the right kidney is mobilised medially and, taking care to avoid damaging the vascular patches, dissection is carried out on the para-spinal muscle, completely detaching the kidney and leaving only the ureter connected.

The ureter is dissected with enough peri-ureteric tissue to preserve vascularity and it is divided as far down as possible (below the level of the pelvic brim). The left kidney is dissected in a similar manner.

Both kidneys are placed on the bench in two separate cold saline containing dishes. The side of the kidney (left or right) should be marked in some way to avoid a mix-up prior to transfer to the transport boxes or perfusion machines.

11.4.1.2.10. Additional vessels and tissue

Additional vessels are required for pancreas and potentially for liver transplantation, and therefore the iliac vessels are retrieved. The iliac arteries are dissected *en bloc*, including full lengths of both internal and external iliac arteries and taking care to avoid cuts or traction injuries during the process. Sometimes this part of the procedure is delegated to the junior surgeon, while the lead surgeon attends to the organs prior to packing. The junior surgeons must be instructed on the importance of careful vascular retrieval and meticulous technique.

The iliac veins are also dissected *en bloc* with similar attention to detail and separated on the bench. If the iliac vessels are not suitable, other vessels such as the carotid artery with its bifurcation, superior mesenteric artery and the first mesenteric branches, or the innominate vessels should be retrieved.

Several lymph nodes should be dissected from the mesentery as they are required for tissue typing and must be shared between all retrieved organs together with samples of spleen.

Note: In cases of pancreas retrieval, parts of spleen for typing should be obtained from the convex side in order to not jeopardise integrity of the pancreatic tail.

11.4.1.2.11. Closure

When the procedure is completed, the operating field must be completely dried and the fluid aspirated. The wound is closed with a herringbone stitch achieving a good cosmetic result.

11.4.1.3. *In situ perfusion*

There are substantial practice variations with regards to the choice of perfusion fluid and the route of administration (portal and aortic *versus* aortic only). Current evidence seems to suggest that, for multi-organ retrievals, aortic-only perfusion is preferred with the University of Wisconsin (UW) solution or similar multi-organ preservation solutions [5, 6]. Around 3-4 L of preservation solution are used during a liver–pancreas–kidney retrieval. The initial 3 L are perfused under pressure, with the remaining litre perfused slowly, to preserve the cold intravascular environment during the cold dissection phase. However, these volumes must be regarded as indicative, and intra-operative evaluation of the venous effluent aspect will guide the actual usage.

It is universally agreed that aortic perfusion should be pressurised in order to achieve reasonable end-organ perfusion. Evidence suggests that pressurised arterial perfusion (e.g. 100-150 mmHg) is associated with less ischaemic-type biliary complications in the liver and fewer primary non-function events [11, 12]. On the contrary, pressurised portal perfusion has a detrimental effect [13] and therefore, if portal perfusion is utilised, it should be under gravity.

Once all organs are placed on the bench, addi-

tional perfusion must be undertaken. This is particularly important for the liver, where portal perfusion takes place on the bench (rather than *in situ*). Bile duct perfusion on the bench must ensure that the effluent is clear of bile.

The pancreas must be gently perfused (unpressurised) via the splenic artery and SMA to confirm the presence of cross-circulation and the patency of portal system, and to ensure that no damage has occurred when the small bowel mesentery has been stapled. The kidneys are also flushed until the renal vein effluent is clear of any residual blood.

11.4.1.4. *Bench surgery*

The purpose of additional bench surgery is to separate the liver–pancreas block if the organs have been retrieved together, to check the quality of perfusion and to inspect the organs for damage and any other unsuspected lesions.

11.4.1.4.1. Separation of the liver–pancreas block

The liver–pancreas block is placed in cold preservation solution in the anatomical position. The dissection is facilitated by the identification of GDA and splenic arteries in the warm phase.

The coeliac axis is dissected from the aortic patch, and the splenic and the GDA are identified in this order. Both arteries are divided and marked as described, preserving an adequate stump with the hepatic arterial tree. The portal vein is then dissected, and particular attention must be paid when exposing the right side of the vein to ensure that no aberrant artery is present.

The portal vein is then divided, sharing its length between the liver and the pancreas, and the remainder of the periportal tissues are divided to complete the separation.

Once separated, the liver and the pancreas are perfused individually as described. The organs are inspected and any damage must be adequately documented.

If identified, any significant injuries that would require reconstruction must be communicated to the implanting team.

11.4.1.4.2. Kidney bench surgery

Each kidney is assessed and the perirenal fat should be partly incised to inspect the quality of perfusion throughout the kidney and to check for the presence of renal lesions. Excess perirenal fat should be removed as it creates an insulation layer that prevents adequate cooling of the kidney in the transport box and renders subsequent bench surgery at the recipient centre more difficult. Preparation of kidney for implantation is not required at this stage.

Sometimes renal fat can be very adherent. In that case, it should not be removed, as in the pressure of the retrieval theatre damage may be caused. However, a message should be passed to the recipient team warning them of the problem.

11.4.1.5. *Packing and transport*

Each organ should be placed in an appropriately sized sterile bag and submerged in preservation solution. The bag is vacuumed and ligated, and may be placed in a suitable bowl to provide extra protection for transport. The bowl is then placed in two additional vacuumed bags surrounded by slush ice prior to being placed in the transport box. The transport box must be large enough to accommodate the bowl in a horizontal position and completely submerged in ice.

11.4.1.5.1. Additional samples

The iliac vessels are separated, and one of each of the iliac arteries and veins is packed in containers with preservation fluid and sent with the liver and the pancreas respectively. Saline-filled pots with six to seven lymph nodes and 1–2 cm^2 spleen sample, as well as blood samples, accompany each organ in the transport boxes.

11.4.1.5.2. Paperwork and documentation

The lead surgeon has the responsibility to ensure that the operation record and all the relevant documents that accompany the organs are completed accurately. Some of the tasks may be delegated, but proper sign-off remains the duty of the lead surgeon. The following is an indicative list of the paperwork required, although requirements may vary across jurisdictions:

- Organ-specific form required by the procurement organisation, detailing retrieval times and place, organs removed, individual organ appearance and injuries, and quality of perfusion. A copy of this form will accompany each organ to the destination centre. In this context, it is best practice to re-evaluate the organ upon arrival before implantation and to exchange this information between implanting team and procurement team. Appendix 22 provides an example from the Netherlands for fully electronic work-up.
- Retrieval team information form, which may be required for audit purposes.
- Operation note, which must be written by the lead surgeon in the donor's case notes. This

should document type of incision, findings at laparotomy, organs removed, additional vessels and tissue recovered, and details of closure.

11.4.2. Controlled donation after circulatory death

This section describes the tasks to be considered from a logistics, technical and practical point of view. For further details about cDCD, refer to section 12.3.

11.4.2.1. *Preparations prior to the withdrawal of life-sustaining treatment*

The surgical team should arrive at the donor hospital with plenty of time ahead of the planned withdrawal time, to enable a review of the donor details, history, consent and all other donor documentation. This will also allow the team to make the necessary preparations for normothermic regional perfusion (NRP) or the hypothermic flush and infusion of preservation fluids. The preparation steps are now explained.

11.4.2.1.1. Setting up perfusion set

A giving set tubing is connected to an 18 Fr catheter (e.g. William Harvey arterial perfusion cannulae) or any appropriately sized catheter for aortic cannulation.

The first litre of preservation solution infused contains 20 000 IU of heparin. Usually four 1 L IV bags of solution are used. IV fluid pressure bags are used to apply pressure only to the aortic perfusion fluids.

Similarly, a giving set tubing is connected to a 16 Fr catheter for portal cannulation, which is primed with preservation solution. The first litre of preservation solution contains 20 000 IU of heparin. Both tubings are clamped for flush control on the surgical field.

There is evidence to suggest that *ante mortem* administration of heparin (in countries where this is permitted) is associated with fewer complications in DCD liver transplantation (Appendix 21).

11.4.2.1.2. Bench set-up

The bench should be set up to receive the liver. A separate bowl is filled with 2 L of sterile crushed saline ice and 1 L of preservation for topical cooling.

A double-balloon triple-lumen (DBTL) catheter can be prepared as an alternative method to cannulate the aorta. The DBTL may be used in case of history of previous thoracic surgery, anticipating a prolonged sternotomy or in the rare cases where the family does not wish for the thorax to be accessed.

11.4.2.1.3. Operative table set-up

The scrub nurse should set up the instrument tray in the order required for a rapid laparotomy and aortic cannulation, to minimise the time taken from cardiac arrest to cold perfusion (knife, scissors, abdominal retractor, aortic cannula, Lahey forceps and cannula ties, automated sternal saw, partially opened Finochetto sternal retractor, long Roberts forceps).

11.4.2.1.4. Team briefing

The surgeon should discuss with the rest of the team the steps of the retrieval process and any potential deviations from a standard DCD retrieval due to specific donor issues (e.g. aortic aneurysm, previous thoracic surgery).

If a thoracic team is present, the abdominal team should discuss the steps of the retrieval process and agree a common strategy to ensure that all organs are retrieved in a rapid and safe fashion.

11.4.2.2. *Definition of ischaemic times*

The outcome of transplantation with organs from cDCD donors is significantly influenced by the length of the warm ischaemia time (WIT). Following the withdrawal of life-sustaining therapies (WLST), several times have been defined:

a. Withdrawal time (agonal phase): the time from WLST to circulatory arrest.
b. Warm ischaemia time, primary (asystolic time): the time from circulatory arrest to *in situ* perfusion.
c. Functional warm ischaemia time (FWIT): the time between the first episode of significant hypoperfusion and *in situ* perfusion [14].
d. Total warm ischaemia: withdrawal time + warm ischaemia time.

The definition of FWIT is yet to be universally agreed, but in general a sustained fall in systolic blood pressure ≤ 50 or 60 mmHg is accepted both in Europe and the United States as the moment that marks a significant hypoperfusion of organs [15, 16]. In addition, the United States guidelines define the total donor WIT as the time from WLST to *in situ* perfusion.

The FWIT that is currently acceptable varies for different organs and range from 30 minutes for the liver and pancreas to 60 minutes for kidneys and lungs [17]. There is a lack of evidence supporting these times and the thresholds for FWIT, and several reports suggest that longer times yield transplantable organs [18, 19]. It is likely that the ability to do *in situ* assessment with NRP, or *ex situ* machine perfusion

assessment will remove the need for decision making based on FWIT.

Following WLST, the donor co-ordinator must communicate the vital signs (blood pressure, mean arterial pressure and pulse) every 5 minutes to the procurement team.

11.4.2.3. *Technique (super-rapid)*

The donor is placed in a supine position and the skin is quickly prepared with antiseptic solution and draped typically with a large single-use light drape to save time. A clear sterile adherent drape is placed over the abdomen and chest to ensure sterility and to secure the drapes.

The standard retrieval procedure derives from the super rapid technique, originally described by Casavilla *et al.* [20]. The procedure begins with a midline laparotomy that extends from the sternal notch to the pubis. The incision is made with a scalpel, as there is no need for diathermy in the absence of circulation. Rapid access to the peritoneal cavity is aided by lifting the abdominal wall. This also minimises the risk of intra-abdominal organ injury during this step. The abdomen is kept open using a large self-retainer retractor that has been prepared half open for speed of insertion.

Following an incision of the peritoneal reflection of the distal ileum and caecum, the small bowel is reflected superiorly, exposing only the area of the aorto-iliac bifurcation enough to rapidly identify and cannulate the distal aorta or the right iliac artery.

Once the aorta is cannulated, cold perfusion begins immediately with preservation solution containing 20 000 IU of heparin. The cannula should be secured in place to avoid displacement. The IVC can be vented in the abdomen or in the chest. The latter is preferable and can be done by opening the diaphragm or with a thoracotomy.

Venous venting should be concomitant with the start of the aortic perfusion, to avoid congestion of the abdominal organs. Copious saline ice slush is placed in the abdomen (paracolic gutters, lesser sac and over the liver) and chest for topical cooling of the organs.

The thoracic cavity is entered via a sternotomy using a Gigli or automated sternal saw. The sternum and ribs are kept apart with a Finochietto retractor, offered half open for speed, the pericardium incised and the right atrium partially divided to improve venous venting. Both pleurae are opened so that the right atrium drains into the large pleural cavities where two pool suction tubes are placed to collect the effluent blood/perfusion solution.

The left lung is lifted, exposing the descending thoracic aorta, which is clamped using a long Roberts clamp. Now that the perfusion fluid will not be wasted in the chest, preservation solution should be infused under pressure, to improve perfusion pressure in the aorta. Perfusion of the aorta by gravity flow only achieves suboptimal pressures in the hepatic artery of 19 mmHg and 16 mmHg, respectively [21].

The portal vein is cannulated via the SMV and perfused with 1 L of preservation solution also containing 20 000 IU of heparin. The SMV is exposed at the root of the mesentery for cannulation below the head of the pancreas, in the groove between the transverse mesocolon and the mesentery of the first loop of the small bowel. IMV cannulation should be avoided, as it is small calibre, provides a slow perfusion and could lead to oedema of the pancreas. The limited data do not show differences between single and dual perfusion; current clinical practice is largely dual aortic and portal vein perfusion (Appendix 22).

In the case of concomitant pancreatic retrieval, the portal vein needs to be directly isolated after division of the common bile duct (CBD) and cannulated approximately 1 cm from the edge of the duodenum. The portal vein should be divided to ensure free drainage and to avoid congestion of the pancreas.

The fundus of the gallbladder is incised, with care taken not to squeeze bile from the gallbladder into the common duct. The gallbladder content is aspirated and the lumen flushed with copious cold normal saline using a bladder syringe. The divided CBD is directly flushed with cold perfusate using a 10 mL syringe with a heparin needle.

The subsequent steps of the procedure are no different from the cold phase dissection used for a rapid retrieval technique in unstable DBD donors. The liver is retrieved first, followed by the pancreas and the kidneys. Some teams advocate the retrieval of liver and pancreas *en bloc* and subsequent separation of the two organs on the bench, though there is no clear advantage for this.

As mentioned, 20 000 IU of heparin must be added to the first litre of perfusate for the portal vein and the first litre of perfusate for the aorta. The latter does not require any drugs to be added to the solution. Usually the flow of perfusate in the portal vein is slowed down after 800 mL to complete 1 L of perfusate portal perfusion *in situ*.

Usually pressure is stopped after the second bag of fluid is through the aorta, and subsequent perfusion is by gravity, to allow cold perfusion of the aorta throughout the entire procedure until organs are removed. However, these steps must be confirmed with the retrieving surgeon.

Several techniques have been described for re-

trieving lungs in suitable cDCD donors. The implications are important and, generally, given the greater tolerance of lungs to warm ischaemia, the thoracic team will allow the liver team to cannulate the abdominal aorta and the portal system whil reintubating the donor and inflating the lungs.

Given the greater tolerance of the lungs to the effect of ischaemia once insufflated with oxygen, the general agreement is that the abdominal organs (liver and pancreas) should be retrieved before the lungs are removed, to minimise the ischaemic time. The lungs can then be retrieved at the same time as the abdominal surgeons proceed with the kidney retrieval.

11.4.2.4. *Modifications to the super rapid technique procedure*

A modification of this technique entails starting with a quick thoracotomy and venting the right atrium to reduce congestion of the abdominal IVC and of the liver in particular. This step may delay aortic cannulation by 2-3 mins. A laparotomy follows with aortic or iliac cannulation and aortic perfusion. After a first rapid cold flush, the supradiaphragmatic aorta is clamped and pressure perfusion begins.

This modified technique of early sternotomy has two advantages:

1. It circumvents aggravating congestion of the liver and abdominal organs, while avoiding venting the IVC in the abdomen and keeping the cavity clean from the warm venous effluent blood.
2. The access to and prompt clamping of the descending thoracic aorta allows for more immediate pressure perfusion of the abdominal organs without wasting the cold perfusion in the chest.

In summary, the modifications of the retrieval procedure reduce liver congestion, improve organ perfusion and facilitate surgical dissection, thus further reducing DWIT.

Other minor changes to the Casavilla technique have been described which use different techniques of securing the aorta, aimed at speeding aortic cannulation.

11.4.2.5. *Organ recovery procedure – thoracic organs*

Upon arrival in theatre, the donor should be re-intubated with a cuffed endotracheal tube and a thorough airway toilet performed (if lungs are being retrieved). Atelectatic lung may be recruited with a single breath (e.g. 25 mmHg pressure for 40 seconds), ideally using the anaesthetic machine which is also useful for maintaining CPAP at 5 cmH_2O and delivering continuous O_2. The time of lung inflation should be noted but cyclical ventilation should be delayed until the chest is open and the aorta clamped. These early manoeuvres lessen the warm ischaemia and allow time for the removal of the liver, which is highly sensitive to warm ischaemia.

The chest is rapidly opened and the lungs are examined for collapse, consolidation, mass lesions and pleural adhesions. The lungs should be tested if there is a suspicion of airways disease, noting the degree of collapse when the lungs are disconnected from the ventilator. The pulmonary artery is then cannulated, and the right ventricle opened to remove clot. Antegrade perfusion should be started as per the practice of the retrieval team. The left atrium or atrial appendage should be widely opened, washing the clot out of the pulmonary veins. Once antegrade perfusion is completed, the pulmonary veins should be cannulated and retrograde perfusion is undertaken until the effluent from the pulmonary artery is clear. The lungs may be removed either collapsed or inflated. The lungs are re-examined after removal and then reinflated for storage on the back table whenever needed.

A large registry study by the International Society for Heart and Lung Transplantation did not find any difference in 5-year recipient survival after lung transplantation with cDCD *versus* DBD lungs [22]. The use of DCD hearts is still limited but rapid removal, followed by *ex situ* normothermic machine perfusion has been proposed by the Sydney group [23].

11.4.2.6. *Organ recovery procedure using normothermic regional perfusion*

Following the Spanish experience in uncontrolled donation after circulatory death (uDCD), several countries have explored the feasibility of normothermic regional perfusion (NRP) in cDCD using similar technology (heat exchanger, oxygenator and pump). NRP allows the *in situ* preservation of organs subject to transplantation with oxygenated blood following the determination of death and prior to organ recovery.

Based on data from preclinical and clinical studies, NRP seems to reverse the metabolic derangements caused by warm ischaemia, re-establishing cellular physiology after energetic depletion and clearing metabolites. This preconditioning effect of NRP may attenuate ischaemia–reperfusion injury. NRP transforms an urgent into an elective recovery procedure, similar to the one in the context of DBD. During NRP, an evaluation of organ viability can take place based on the behaviour of certain biochemical

parameters, as already mentioned. These advantages of NRP should be translated into improved outcomes after transplantation. Until recently, however, evidence of such benefits was scarce.

Two recently published multicentre retrospective experiences have shown the benefits of NRP in liver transplantation from cDCD donors. Hessheimer *et al.* [24] analysed the outcomes of cDCD liver transplants performed in Spain from June 2012 to December 2016. The median donor age was 56 years. The authors compared the evolution of 95 recipients of cDCD livers obtained with NRP *versus* 117 livers recovered through the standard rapid recovery technique. NRP significantly decreased the rate (OR = odds ratio, CI = confidence interval and p = p value) of

- overall biliary complications (OR 0.14; 95 % CI 0.06-0.35, p < 0.001),
- ischaemia-type bilary lesions (ITBL) (OR 0.11; 95 % CI 0.02-0.57; p = 0.008) and
- graft loss (HR 0.39; 95 % CI 0.20-0.78; p = 0.008).

The study revealed that the donor age of cDCD liver donors could be expanded safely with NRP, as suggested by other authors. An initial UK series of 11 patients receiving cDCD liver transplantation following NRP had one reported case of primary non-function (PNF), an early allograft dysfunction (EAD) rate of 36 % and no incidence of ischaemic cholangiopathy [25].

A subsequent UK two-centre study of cDCD liver transplantation following NRP (n = 44) compared to static cold storage (SCS) controls (n = 185) reported a significantly lower incidence of EAD (12 % *versus* 32 %, p = 0.008) and anastomotic stricture rate (7 % *v.* 27 %, p = < 0.0001), with no cases of ischaemic cholangiopathy in the NRP arm (0 % *v.* 27 %, p = < 0.0001). A lower rate of 30-day graft loss was reported in the NRP group (2 % *v.* 12 %, p = 0.06) [26]. After adjusting for other factors in a multivariable analysis, NRP remained significantly associated with freedom from ischaemic cholangiopathy (p = < 0.0001). Two studies from the University of Wisconsin on five and 13 cDCD liver transplants performed following NRP reported a 1-year graft survival of 86 %, a two-year graft-survival of 71 % and a 14 % PNF and biliary stricture rate [27, 28]. A series of 20 DCD liver transplants performed in Italy with NRP reported no significant difference in 1-year patient (95 % *v.* 94 %, p = 0.94) or graft survival (85 % *v.* 91 %, p = 0.20) compared to DBD grafts, despite the extended stand-off period of 20 minutes following donor asystole. The ischaemic cholangiopathy rate was 10 %, but no recipients underwent retransplantation due to biliary complications [29].

Although no prospective randomised trial has been conducted to confirm these observations, these two studies suggest that NRP during organ recovery from cDCD donors leads to superior liver transplant outcomes compared with conventional organ recovery.

Information on the impact of NRP on cDCD kidney transplantation is scarce. Unpublished Spanish data on 1 582 recipients of cDCD donor kidneys subject to NRP (485) *versus* the standard recovery technique (n = 1.097) reveal that NRP is associated with a significantly lower incidence of delayed graft function (32 % *v.* 48.6 %), defined by the need of dialysis during the first week after transplantation. However, no significant benefits are observed in terms of PNF and graft survival in the short term.

Three other studies have reported on kidney transplant outcomes following NRP in cDCD donors with delayed graft function (DGF) rates of 18 % [30], 31 % [25] and 40 % [26]. Three further studies have reported on outcomes following NRP in cDCD kidney transplantation in comparison to DBD control groups [27, 31-32]. In a study from the University of Wisconsin there was no statistically significant difference in DGF (8 % *v.* 24 %, p = 0.1) in controlled DCD kidneys following NRP (n = 24) compared to DBD kidneys (n = 100) [27]. A second study from Spain also showed that there was no statistically significant difference in DGF (27 % *v.* 33 %, p = 0.56) or 1-year graft survival (92 % *v.* 97 %, p = 0.32) in cDCD kidneys following NRP (n = 37) compared to DBD kidneys (n = 36) [31]. The largest study to date reports the use of NRP followed by hypothermic machine perfusion (HMP) according to the National Protocol for kidneys from cDCD donors in France (n = 92) and compares the outcomes to kidneys from DBD donors (n = 5176) [32]. This study reported significantly lower levels of DGF in cDCD kidneys following NRP when compared to DBD kidneys (9 % *v.* 19 %, p = < 0.05) [32]. In Italy, where declaration of circulatory death is based on absence of electrical activity and requires a minimum no-touch period of at least 20 minutes [33], a series of 10 kidneys from cDCD donors using NRP and oxygenated HMP reported a DGF rate of 30 % and no cases of PNF [34].

The process of organ recovery described above is modified to enable a period of NRP.

Certain *ante mortem* interventions are permitted in some but not all European countries [35]. In those countries where these interventions are allowed by local legislation, heparin can be administered prior to withdrawal. Alternatively, 25 000-50 000 IU

of heparin should be added to the NRP priming solution. Some countries also allow the *ante mortem* cannulation of femoral vessels or introduction of sheets in order to facilitate the immediate initiation of NRP following the determination of death. For example, *ante mortem* heparinisation and vessel cannulation are allowed in Spanish guidelines if no contraindications are identified (e.g. heparinisation would not be allowed if there is a haemorrhagic lesion) and if specific informed consent is obtained [36]. A similar protocol has been also developed in the United States [28]. Although both interventions are clinically thought to yield higher numbers and quality of organs for transplantation, there is still not clear evidence of the superiority of using these *ante mortem* interventions.

Where *ante mortem* cannulation of femoral vessels is performed (see §12.2.4.1.1), an aortic balloon is usually used to restrict preservation to the abdominal cavity [37]. The correct position of the aortic balloon must be radiologically confirmed prior to WLST. The balloon will be inflated after death has been determined, immediately before initiating NRP. Two arterial lines, one from the femoral arterial cannula and the second from the left radial artery, should be monitored during NRP to ensure an adequate blocking of the aorta. With a correct occlusion, the arterial pressure from the left radial artery will be absent, while the pressure from the femoral arterial cannula is maintained as a continuous, non-pulsatile pressure, as it is provided by the extracorporeal circulation with membrane oxygenation (ECMO) device [38].

Where *ante mortem* cannulation of femoral vessels is not performed and once death has been confirmed, the donor is taken to theatre and a midline incision (xiphoid to pubis) is undertaken. The infrarenal IVC is dissected and encircled using a vascular snugger. The distal end is clamped or ligated. The venous cannula is inserted into the IVC. The tip should sit just below the diaphragm to allow the clamping of the suprahepatic IVC without compromising the venous return in the circuit. The venous limb of the circuit is then connected to the cannula. The distal infrarenal aorta is identified and slung using a vascular snugger. The distal aorta is cross-clamped or ligated. The aortic cannula is inserted, checking the proximal position of the tip. The cannula is secured in place with the vascular snugger and connected to the arterial limb of the circuit. A rapid sternotomy is carried out using either a power saw or Gigli saw. The thoracic aorta is clamped below the level of the left subclavian artery. An alternative approach would be to insert an aortic endo-clamp in the descending thoracic aorta and commence the NRP before undertaking the sternotomy. This approach would allow the cardiothoracic team to undertake the sternotomy and mobilise the lung and clamp the descending aorta (if simultaneous lung recovery).

At this point a cannula is inserted in the ascending aorta to monitor for absence of flow to the brain and now the NRP circuit can be started.

Once the NRP is established, meticulous haemostasis must be ensured from the abdominal wound edges, sternotomy and retroperitoneal tissues disrupted during aortic and IVC cannulation. It is also paramount that thoracic teams are meticulous in avoiding blood loss.

NRP is usually performed for two hours in cDCD, although the optimal duration remains to be determined. The pump parameters are yet to be fully established but the United Kingdom experience suggests a pump flow of 2-3 L/min (up to 5 L/min if thoraco-abdominal), temperature between 35.5 °C and 37.5 °C, 2L/min air (or air/O_2 mix as required to maintain venous HbO_2 saturations between 60 % and 80 %), a pH of 7.35-7.45 (administer bicarbonate as required) and a haematocrit > 20 % [25].

During this period, serial blood samples are taken to assess the function and cellular damage of the liver and pancreas. Organ mobilisation and preparation for the cold phase can be undertaken, following the same steps as a DBD recovery.

Once NRP is completed, cold *in situ* perfusion is instituted and organ recovery continues as described above.

If thoracic (lung) recovery is planned in a donor where NRP is undertaken [37], the suprahepatic IVC is clamped at the cavo-atrial junction. The ascending aorta is clamped, the main pulmonary artery (PA) is cannulated for cold flush-perfusion and the left atrial appendage is vented widely.

Ventilation is started at half tidal volume with 5 cmH_2O PEEP and FiO_2 0.4 and pulmonary flush with cold Perfadex solution commenced. The pleurae are opened widely and lungs inspected and palpated, ensuring adequate delivery of flush and topical cooling with copious volumes of 4 °C saline. While waiting for the pulmonary flush to be delivered, the superior vena cava is ligated and divided just below the azygos take-off and the systemic connections of the heart are disconnected, leaving the IVC clamped within the pericardium. The division of the main vessels proximal to the clamps ensures that there is no blood loss, to avoid compromising the NRP flow.

Once the cold pulmonary flush is completed, the main PA is divided just proximal to its bifurcation. The lungs are allowed to deflate at this stage. The left atrium is divided, leaving behind an adequate

cuff for the lungs and the excised heart is removed for later recovery of heart valves. The pericardium above the diaphragm is incised, the inferior pulmonary ligaments are divided and the plane up to and behind the trachea is developed. The trachea is dissected bluntly circumferentially in the space between the superior vena cava and aorta, and pulled down to gain as much length as possible. The endo-tracheal tube is withdrawn, a breath with 50 % tidal volume is delivered and the trachea is stapled with the bronchial stapler and divided above the staple line. The lung block is removed and complete haemostasis of the mediastinum should be ensured. Retrograde pulmonary venous flush of the lungs is performed with 1 000 mL of preservation solution on the back-table at the donor site [39].

Abdominal NRP continues for the planned duration as detailed above.

An alternative approach is currently under investigation extending the NRP to involve the thoracic organs (TA-NRP) but excluding the cerebral circulation. This approach allows the recovery of lungs as well as hearts [40, 41]. TA-NRP is being used in the UK, Belgium and more recently in Spain as a strategy to allow the validation and preservation of hearts of cDCD donors. In the British experience, most hearts recovered by using TA-NRP have been followed by *ex situ* machine perfusion. To the best of our knowledge, five heart transplant procedures have taken place in the world with good results with the use of TA-NRP without *ex situ* machine perfusion. Given the high cost of *ex situ* machine perfusion, unaffordable in many settings, TA-NRP may become a way of making heart transplantation from cDCD donors economically feasible in some countries.

Manara *et al.* reviewed the current TA-NRP protocol and suggested the following logical model [42]. If:

1. Death in DCD, as in everyday clinical practice, is defined by the permanent cessation of circulation to the brain, and
2. After the confirmation of death in DCD and prior to starting NRP, the surgical act of ligating or dividing the aortic arch vessels in TA-NRP, or occluding the descending thoracic aorta in A-NRP, is medically and ethically acceptable, and
3. In order to adhere to the principle of permanence for death, the absence of potential for brain perfusion can be ensured by the refinements outlined in this paper.

Then:

1. Restarting the circulation to the thoracic and/or abdominal cavities after death does not invalidate the definition of death in DCD organ retrieval,
2. Restarting the heart in the donor's body after death does not invalidate the definition of death when brain perfusion is excluded, and
3. Abdominal and TA-NRP may be considered permissible.

In a study from Papworth, 12 DCD heart transplants recovered with TA-NRP with *ex situ* NMP were compared to 14 hearts recovered with DPP and *ex situ* NMP and DBD heart transplants (n = 26). There were no significant differences in the outcomes between the two approaches or in comparison to DBD heart transplantation [43]. In a recent review article the experience with DCD heart transplantation with these techniques was updated to 39 cases with a recipient survival to discharge rate of 93 % [44]. Recently, several additional cases of TA-NRP followed by cold storage and transplantation, without *ex situ* NMP were described, with good outcome [41, 45].

The bithermic/dual technique approach used in uDCD can also be used in the cDCD setting, but experience is limited (see §12.2.4.1.1) [46].

11.4.2.7. *Organ preservation – in situ cold preservation*

A variety of preservation solutions can be used. There are no randomised controlled trials of preservation solution in cDCD donors, but several solutions have been designed to minimise the detrimental effects of cold ischaemia and reperfusion. Often used solutions for abdominal organ preservation are UW solution, HTK solution, Celsior and IGL-1. Different studies have been undertaken to investigate the differences in performance (organ cooling, delayed graft function) of these solutions in regard to different organs [47, 48]. An indicative total volume of 4-5 L is used during multi-organ abdominal recovery, adjusting this according to the instructions of the manufacturer and clinical situation [49, 50].

It is important that the initial bags of perfusion solution contain heparin (20 000 IU/L perfusion) and if dual perfusion is used (as is the case for the liver), both must contain heparin.

In situ lung preservation uses low-potassium dextran glucose solution supplemented with 3.6 % THAM 3.3 mL, 0.6 mL CaCl + 2.5 mL prostacyclin per litre or Celsior with a minimum 60 mL/kg volume infused.

11.4.2.8. *Organ preservation – in situ normothermic regional perfusion*

The optimal priming solution for NRP has not been fully established. An example combination includes [25]:

- Bicarbonate 8.4 %, 1 mL/kg
- Compound Sodium Lactate solution – 1 000 mL
- Heparin – 50 000 IU
- Fluconazole – 200 mg
- Meropenem – 500 mg
- Vancomycin – 1 g
- Methylprednisolone – 1 g
- Pancuronium – 12 mg

11.4.3. Uncontrolled donation after circulatory death

For uDCD procedures applicable to *in situ* preservation and organ recovery, including abdominal organs and lung preservation, see Chapter 12, §12.2.4.

11.4.4. Organ evaluation during organ procurement

11.4.4.1. *DBD organ assessment*

Donor and organ evaluation are based on the review of the past and present medical history and of risk behaviours of the potential donor, plus a physical examination and complementary tests. Available medical records and charts must be carefully reviewed. A dedicated and guided interview with the relatives should always take place for the assessment of the donor's suitability.

In addition, the biochemistry trends prior to donation should guide decisions whether to accept the organs. The advantage of a DBD donor is that it enables the surgeon to evaluate the perfusion of the organs prior to cross-clamping as well as during the cold perfusion phase. Both are useful adjuncts in assessing the suitability of the organs. (See also Chapter 7, Specific organ characterisation, assessment and selection criteria.)

11.4.4.2. *cDCD organ assessment*

The evaluation of cDCD donors starts with a detailed medical and socio-demographic history that the donor co-ordinator should obtain from all relevant sources (notes, interviews with treating physicians, family and general practitioners etc.). Factors such as age, duration of hospital stay and ICU admission, the use of high-dose vasopressors and the absence/presence of infection are highly relevant for the decision whether to utilise the organs.

Based on these characteristics, the 'ideal' cDCD donor can be defined as a donor of age < 50 years with a weight < 100 kg, a short ICU stay (< 5 days) and a WIT < 20 minutes [52].

The absolute contraindications to DCD organ donation are the same as those for DBD (see Chapter 6, General donor characterisation, assessment and selection criteria), e.g. invasive or haematological malignancy, untreated systemic infection, prion disease and HIV disease.

Biochemistry samples must be obtained prior to donation and, if relevant, compared with other samples taken during admission (especially for donors with a history of out-of-hospital cardiac arrest or a history of hanging).

The procurement surgeon must assess the quality of the perfusion, the appearance and the anatomy of the organs *in situ* and on the bench. Unlike DBD, where assessment includes a period of circulation, cDCD assessment is much more difficult and is subjective to the surgeon's experience.

The decision to utilise the cDCD organs should also take into account the recovery factors such as duration of WIT.

NRP offers the additional benefit of in-depth *in situ* macroscopic assessment of the organs' appearance, including that of the small bowel and gallbladder mucosa (both highly sensitive to ischaemic damage). NRP also offers the possibility of evaluating organ function, based on serial biochemical and blood gas analyses undertaken during the procedures (every 30 minutes). Given the limited experience, further clarification of the factors that are important is required.

11.4.4.3. *Organ-specific evaluation criteria in cDCD*

Once a patient's suitability to donate has been established, additional evaluation criteria come into consideration for specific organs. All organ-specific issues are discussed in section 12.3.9. These may relate to donor's age, the timings of recovery (such as the length of WIT, the agonal phase duration or the length of predicted cold ischaemic time) and specific pre-existent comorbidity (such as cardiovascular disease, hypertension, diabetes or liver disease).

11.4.4.4. *uDCD organ assessment*

Evaluation and validation of uDCD donors is done according to general inclusion criteria for organ donation, along with the specific selection criteria for each organ (see Chapter 6, General donor characterisation, assessment and selection criteria and Chapter 7, Specific organ characterisation, assessment and selection criteria). Besides, criteria specific for uDCD must be taken into account, as

summarised in Table 12.3 (§12.2.1). For organ-specific criteria, refer to section 12.2.6.

11.5. Preservation during transport

Currently, the accepted method for *ex situ* preservation is static cold storage (SCS). Novel approaches based on *ex situ* machine perfusion of isolated organs are currently being explored and some have already been implemented in practice [53]. Although no universal nomenclature is in use, in the context of deceased organ donation *ex situ* is the preferred terminology over *ex vivo*, given that machine perfusion occurs after the organs have been removed from the body of a deceased donor [54]. A number of perfusion variables including temperature (normothermic, subnormothermic or hypothermic), oxygen delivery and perfusate (blood-based, blood analogues or specifically designed media) are currently being investigated [55].

11.5.1. Kidney transplantation

The key performance indicators following kidney transplantation are graft utilisation, immediate *v.* delayed graft function (DGF) *v.* primary non-function (PNF), graft survival, patient survival and 1-year graft function (eGFR and creatinine) [56]. The standard technique for kidney preservation is still SCS in most centres.

11.5.1.1. *Hypothermic perfusion strategies*

Standard HMP involves the kidney being connected to a perfusion device and a cold acellular preservation solution being pumped continuously through the renal vasculature at temperatures in the range 1-10 °C [57]. A number of meta-analyses have been published comparing HMP kidney preservation with SCS in kidneys recovered from extended criteria donors [58], DCD donors [59, 60] and across all donor types [60-65]. All these meta-analyses have described a significant reduction in either the reported odds ratio (OR) or risk ratio (RR) of DGF (effect sizes ranging from 0.6 to 0.8) following HMP, but none have reported a significant reduction in PNF [58-65]. Only one meta-analysis of extended criteria donors reported improved graft survival in kidneys following HMP compared to SCS at 1 year (OR 1.12, 95 % CI 1.03-1.21, p = 0.005) [58]. Similarly, there is a single meta-analysis reporting improved graft survival at 3 years across all donor types (RR 1.06, 95 % CI 1.02-1.11, p = 0.009) [65]. A recent Cochrane Review concluded that HMP is superior to SCS in both DBD and DCD kidney transplantation, even when assessing only studies that have been published in the last decade. However, because kidneys from DCD donors have an increased risk of DGF, the number needed to treat to prevent one episode of DGF is less for DCD kidneys (7.26 *versus* 13.60 in DBD kidneys) [62].

A major randomised controlled trial (RCT) of 336 consecutive deceased donors in the Eurotransplant region that randomised in a paired design one kidney from each donor to HMP or SCS reported a significant reduction in DGF (adjusted OR 0.57, 95 % CI 0.36-0.88, p = 0.01) and 1-year graft failure (adjusted OR 0.52, 95 % CI 0.29-0.93, p = 0.03) with HMP [57]. The reduction in DGF with HMP was confirmed in an independently powered extension of this RCT into 82 DCD donors with 164 kidney transplants (adjusted OR 0.43, 95 % CI 0.20-0.89, p = 0.025) [66], and another independent study of 91 extended criteria DBD donors with 182 kidney transplants (adjusted OR 0.46, 95 % CI 0.21-0.99, p = 0.047) [67]. The sub-analysis of extended criteria DBD donors also reported that 1-year death censored graft survival was significantly higher with HMP compared to SCS (92 % *v.* 80 %, p = 0.02; adjusted HR for 1-year graft loss 0.35, 95 % CI 0.15–0.86, p = 0.02) [67]. In the DCD population, a significant reduction in DGF was observed in the HMP group (54 % *v.* 70 %; p = 0.007) but no significant difference was seen for 1-year graft survival between HMP and SCS groups (94 % *v.* 95 %) [66].

In contrast to the DCD study in the Eurotransplant region, an RCT comparing HMP with SCS in DCD kidneys conducted in the UK and analysed by sequential analysis was stopped due to futility (DGF rate HMP 58 % *v.* SCS 56 %) [68]. There are a number of differences between these RCTs, most notably that in the UK trial kidneys were not preserved with HMP from the time of procurement and underwent an initial variable-length period of SCS. In the UK trial there was also fixed control preservation fluid in the SCS group while in the European RCT both HTK (76 %) and UW solution (22 %) were used [69]. Furthermore, the DGF rate for DCD kidneys subjected to SCS was lower in the UK study than in the European DCD extension study (DGF 56 % in the UK *v.* 70 % in the European study) but DGF rates after HMP were similar in the UK (58 %) and European (54 %) trials [84].

In a recent analysis of the NHSBT database from 2007-15, DGF rates were significantly lower in kidneys preserved with HMP compared with SCS (34 % *v.* 42 %, p = < 0.001; adjusted OR 0.65, 95 % CI 0.53-0.80, p = < 0.001) with no difference in graft survival (adjusted hazard ratio 0.88, 95 % CI 0.70-1.10, p = 0.263) [70]. In a recent single-centre retrospec-

tive study from the West London Renal Transplant Centre, pre-implantation HMP following SCS (n = 33) decreased DGF (24 % *v.* 48 %, p = 0.04) compared to SCS alone (n = 33) [71]. A further paired kidney analysis from Germany reported a reduced rate of DGF (12 % *v.* 21 %, p = 0.38; adjusted OR 0.28, 95 % CI 0.07-0.94, p = < 0.04) with pre-implantation HMP (n = 66) compared to SCS (n = 43) [72]. Currently there is an ongoing UK trial replicating the EuroTransplant methods (ISRCTN 50082383).

Two further RCTs of the Consortium for Organ Preservation in Europe (Cope; funded by the EU 7th Framework Programme) recently have completed their recruitment assessing standard HMP *v.* oxygenated HMP. One RCT has randomised kidneys from extended criteria DBD donors to oxygenated HMP after SCS *v.* SCS alone with graft survival at one year as a primary endpoint and analysis currently being performed (Cope-Pomp, ISRCTN 63852508). The second Cope RCT has randomised kidneys in a paired design from cDCD donors older than 50 years to either oxygenated HMP (n = 106) or standard HMP (n = 106) with eGFR as its primary endpoint (Cope-Compare, ISRCTN 32967929). The results of the Cope-Compare study have been reported at the American Transplant Congress in May 2019, showing a significant reduction in biopsy-proven acute rejection rate (14 % *v.* 28 %, p = 0.01), reduced graft loss (3 % *v.* 10 %, p = 0.021) and on sensitivity analysis a significantly higher eGFR (47.6 *v.* 42.6 mL/min/1.73 m^2, p = 0.035) at 1-year follow-up for kidneys perfused with oxygenated HMP. No statistically significant difference was seen as regards DGF and PNF rates between the two methods of cold perfusion in these large groups of older DCD donors (oxHMP *v.* sHMP: DGF 38 % *v.* 38 % | PNF 3 % *v.* 5 %) [73].

11.5.1.2. *Ex situ normothermic perfusion strategies*

Ex situ normothermic machine perfusion (*ex situ* NMP) of kidneys involves perfusion with an oxygenated red cell-based plasma-free perfusate. A study of pre-implantation *ex situ* NMP of expanded criteria donor kidneys (n = 18) using paediatric cardiopulmonary bypass technology compared to matched control kidneys preserved with SCS (n = 47) reported a significant reduction in DGF (6 % *v.* 36 %, p = 0.01) with no difference in graft survival at 1 year (100 % *v.* 98 %, p = 0.51) [74]. *Ex situ* NMP is a technically challenging technique. The Cambridge group reported the assessment by *ex situ* NMP of 10 declined DCD kidneys, five of which were transplanted, and four had initial graft function [75].

More recently, Guy's Hospital in London and the Freeman Hospital in Newcastle reported their initial experience with *ex situ* NMP performed on 14 kidneys from 12 donors, with 12 kidneys transplanted into 10 recipients (two dual grafts). There were no cases of PNF, three patients (30 %) experienced DGF and graft survival was 100 % at 1 year. There were seven donors, of whom one kidney received SCS and *ex situ* NMP, and the other received SCS alone. Although there was a trend towards lower DGF and PNF rates in the *ex situ* NMP group, this did not reach statistical significance [76]. A Dutch group from Erasmus MC University Medical Centre in Rotterdam also reported their experience with NMP performed on 11 kidneys from DCD donors and transplanted into Eurotransplant Senior Program recipients. There were no cases of PNF, four patients (36 %) experienced DGF and death-censored 1-year graft survival was 91 %. There was a not-significant trend towards lower PNF and DGF rates in the NMP group in comparison to the historical control group [77].A multi-centre RCT (ISRCTN 15821205) of pre-implantation *ex situ* NMP for 60 mins (n = 200) compared to SCS (n = 200) in kidneys from cDCD donors is currently recruiting in the UK and is estimated to complete in 2020 [78].

11.5.2. Liver transplantation

The key performance indicators following liver transplantation are graft utilisation, immediate *v.* early allograft dysfunction (EAD) *v.* PNF, hepatic artery thrombosis, biliary complications including ischaemic cholangiopathy, graft survival, patient survival and retransplantation. The standard technique for liver preservation is still SCS in the vast majority of centres.

11.5.2.1. *Hypothermic perfusion strategies*

Hypothermic liver perfusion can be accomplished either via the portal vein (PV) alone or through the PV and hepatic artery (HA) (dual perfusion). As a strategy, HMP has been extensively studied in the context of kidney transplantation. In liver transplantation, the feasibility of end ischaemic dual HMP using a modified bypass device was demonstrated in a case-matched series of HMP preserved DBD grafts (n = 20) compared with SCS (n = 20) [79]. There were no cases of PNF in either group but recipients in the HMP arm demonstrated a lower peak of AST (1 154 *v.* 3 339 IU/ml, p = 0.011), shorter length of hospital stay (11 *v.* 15 days, p = 0.006) and lower incidence of EAD (5 % *v.* 25 %, p = 0.08). A subsequent case-matched series by the same group, comparing declined livers undergoing HMP (n = 31) to extended criteria liver grafts preserved with SCS (n = 50), showed a lower incidence of biliary complications (including strictures

and leaks) within the first year (13 % *v.* 43 %, p = 0.02) and reduced hospital stay (16 *v.* 20 days, p = 0.001), without any difference in PNF (3 % *v.* 7 %, p = 0.61), EAD (19 % *v.* 30 %, p = 0.38) or 1-year patient survival (84 % *v.* 80 %, p = 0.76) [80].

Hypothermic oxygenated perfusion (HOPE) seeks to extend HMP by oxygenating standard machine perfusion fluid to restore mitochondrial function with perfusion via the PV alone. In contrast, dual flow hypothermic oxygenated perfusion (D-HOPE) cold machine preservation solution is pumped via the PV and the HA into the liver and has been postulated to optimise oxygen delivery to the biliary system, although evidence that dual perfusion is superior is lacking [81]. One matched case-series in DCD livers (25 HOPE preserved livers from Zurich *v.* 50 SCS livers from Rotterdam and Birmingham) reported that patients in the HOPE arm had significantly lower peak ALT (1 239 *v.* 2 065 U/L, p = 0.02), developed fewer biliary complications (20 % *v.* 46 %, p = 0.04), with a reduced incidence of ischaemic cholangiopathy (0 % *v.* 22 %, p = 0.02) and improved 1-year graft survival (90 % *v.* 69 %, p = 0.04) but in the context of shorter cold ischaemic times (3 h *v.* 6.5 h, p = 0.01) [82]. After five years of follow-up graft survival was significantly better in the HOPE group compared to the SCS group (94 % *v.* 78 %, p = 0.024) [83].

A further prospective case control study compared DCD livers receiving D-HOPE (n = 10) to SCS (n = 32) [81]. This study showed reduced peak ALT (966 *v.* 1 858 U/L, p = 0.006), peak bilirubin (1.0 *v.* 2.6 mg/dL, p = 0.04) but no statistically significant difference in 1-year graft (100 % *v.* 67 %, p = 0.052) or patient survival (100 % *v.* 85 %, p = 0.21).

Another alternative for oxygen delivery is persufflation, whereby oxygen gas is passed directly through vasculature into the organ during SCS. Oxygen persufflation has been applied in Germany to a small number of marginal grafts (n = 5) with 100 % graft and patient survival at 2-year follow-up. This approach is currently being compared to SCS in a single centre RCT (ISRCTN00167887) aiming to recruit 116 patients [84].

11.5.2.2. *Ex situ normothermic perfusion strategies*

The suggested standard abbreviation for *ex situ* normothermic machine perfusion of the liver is *ex situ* NMP [54]. This technique mandates dual perfusion to mimic normal liver physiology and meet metabolic demands. NMP can be instituted upon procurement at the donor centre or upon the arrival of the liver graft in the recipient centre.

A number of pilot studies initially demonstrated the feasibility of NMP in DBD, DCD and discarded livers [85-87]. A phase 1 two-centre study demonstrated feasibility, safety and potential benefits in individual extended criteria donor livers [81]. A subgroup analysis of six of 20 livers identified more stable post-reperfusion haemodynamic parameters with a decrease in inotrope use during reperfusion [88]. As part of Cope, a subsequent major international multi-centre RCT of NMP, conducted in DBD and DCD livers from the time of procurement, reported that the NMP group (n = 121) compared to the SCS group (n = 101) had lower peak AST (485 *v.* 974 U/L, p = < 0.0001) and significantly lower rates of EAD (10 % *v.* 49 %, p = < 0.001). This was achieved despite a lower discard rate (12 % *v.* 24 %, p = 0.008) and significantly longer preservation times (714 *v.* 465 mins, p = < 0.001). There was no significant difference in non-anastomotic biliary strictures (ischaemic cholangiopathy) (DBD 7.4 % *v.* 5.4 %, p = 0.68; DCD 11.1 % *v.* 26.3 %, p = 0.18), anastomotic biliary strictures (DBD 40.7 % *v.* 41.8 %, p = 0.91; DCD 48.1 % *v.* 57.9 %, p = 0.52), 1-year graft survival (95 % *v.* 96 %, p = 0.71) or 1-year patient survival (95 % *v.* 96 %, p = 0.67) [89].

An alternative and logistically less challenging approach is to undertake NMP pre-implantation upon the arrival of the graft in the implanting centre. A study from Birmingham described successful transplantation of five discarded livers after a period of NMP and suggested several criteria for organ viability based on perfusate pH and lactate, bile production, flows and graft perfusion. All five recipients were reported well with normalised liver tests at a median follow-up of seven (range 6-19) months. These viability criteria could therefore identify extended criteria donor grafts that can be utilised safely, potentially eliminating the risk of PNF [85]. The initial viability criteria have since been modified by the addition of measurement of bile pH while the liver is on the NMP device [90]. However. these require validation in larger trials.

In a study from Cambridge 12 declined livers were transplanted after a period of NMP. The first six livers were perfused at high oxygen tensions and were complicated by post-reperfusion syndrome and vasoplegia in the recipient, complications that were not seen when the oxygen tension was lowered to physiological levels [91]. Outcomes were compared with a contemporaneous cohort of 24 other SCS livers and were found to be similar in terms of 1-year graft survival (83 % NMP *v.* 88 % SCS), 1-year patient survival (92 % NMP *v.* 96 % SCS) and rate of ischaemic cholangiopathy (27 % NMP *v.* 29 % SCS). In a subsequent study from Cambridge 22 declined or high-risk livers were transplanted after NMP with an ischaemic

cholangiopathy rate of 18 %. Whilst NMP pre-implantation was associated with an increased organ utilisation and rescue of organs that would otherwise have been discarded, there was no impact on the incidence of ischaemic biliary complications [90].

Controlled oxygenated rewarming from 10 °C to 20 °C over 90 minutes has been proposed to gradually re-warm the liver and thus be less physiologically stressful. In one study of six DBD liver graft recipients compared with 106 historical DBD controls, controlled oxygenated rewarming was associated with lower peak AST (564 *v.* 1 204 U/L, p = 0.02) [92]. Using a combined resuscitation and viability testing protocol of sequential DHOPE, controlled oxygenated rewarming, and NMP using a new haemoglobin-based oxygen carrier-based perfusion fluid, five of seven livers from declined DCD donors were transplanted with a 3-month graft survival of 100 %. The use of a synthetic oxygen carrier for end ischaemic NMP has the potential advantage of being able to perform NMP with gradual rewarming, something not possible if blood is used as a perfusate [93].

11.5.2.3. *Pancreas transplantation*

The key performance indicators following pancreas transplantation are graft utilisation, graft thrombosis, graft pancreatitis, early graft failures, graft survival and patient survival. The standard technique for pancreas preservation is SCS.

The pancreas is a low-flow organ with complex vascular anatomy that makes optimal perfusion parameters difficult to obtain [94]. As such, experimental work in terms of pancreas perfusion is still ongoing prior to application in clinical practice. One recent study reported successful isolation of functional islets from two of ten discarded pancreases (five DBD and five DCD) after a period of continuous HMP with a dual perfusion system through the mesenteric and splenic arteries [95]. Another study from Imperial College in London placed discarded organs on a normothermic circuit (to mimic transplantation) after a period of HMP and found two of three discarded organs were functional in terms of insulin production [96]. In a study from France, seven discarded human pancreases have undergone HMP for 24 hours with reducing resistive index for the first 12 hours followed by stabilisation of perfusion pressures without developing oedema. Post-perfusion biopsy samples revealed normal staining for insulin, glucagon and somatostatin [97].

Pancreas preservation by oxygen persufflation in combination with SCS (n = 13) has been compared to SCS alone (n = 11) and reported improved β-cell function after islet cell isolation [98]. In a further study, the feasibility of *ex situ* NMP (paediatric cardiopulmonary bypass technology) in declined human pancreases (n = 5) using warm oxygenated packed red blood cells for 1-2 hours has been demonstrated by insulin secretion from the majority of perfused organs (n = 4/5) [99]. Other than successful solid organ pancreas and islet transplantation following NRP [25, 28, 31], to date there have been no reports of pancreases transplanted into a recipient following novel preservation strategies. The Achilles heel of pancreas preservation is damage to the exocrine cells, releasing digestive enzymes and proteases resulting in post-transplant pancreatitis, something that has yet to be overcome.

11.5.2.4. *Cardiac transplantation*

The key performance indicators following cardiac transplantation are graft utilisation, primary non-function, need for mechanical support, graft survival and patient survival. The standard technique for cardiac preservation is SCS for DBD donors and *ex situ* NMP for DCD donors.

Whilst *ex situ* hypothermic heart perfusion is still under development [100], *ex situ* NMP has been implemented clinically. PROCEED II (NCT00855712) was a multicentre RCT that compared 67 standard criteria DBD heart transplants after *ex situ* NMP with SCS (n = 63) and reported similar outcomes in terms of 30-day patient/graft survival rates (94 % *v.* 97 %, p = 0.45) and cardiac-related severe adverse events (13 % *v.* 14 %, p = 0.90). Five hearts were not transplanted in the *ex situ* NMP group on the basis of lactate profile [101]. In a single-centre study (n = 26) from Harefield, *ex situ* NMP has been reported to facilitate transplantation of hearts not initially considered suitable for transplantation or to be used for higher-risk recipients with only one reported death (3.8 %) and preserved allograft function in 92 % of patients [102].

DCD heart transplantation has been one of the most important developments in recent years, with the potential to significantly increase the number of heart transplants undertaken and a significant reduction in waiting list mortality [103]. The first report of successful DCD heart transplantation using *ex situ* NMP was described in 2015 [41], and further case series of DCD heart transplants have followed [104, 105]. At present, two methods for heart recovery are explored: direct procurement and perfusion (DPP), which requires a rapid cooling and procurement of the heart with collection of blood from the donor with which to prime the OCS system, and thoracoabdominal NRP (TA-NRP).

11.5.2.5. *Lung transplantation*

The key performance indicators following lung transplantation are graft utilisation, primary graft function *v.* primary graft dysfunction, unplanned extracorporeal membrane oxygenation support, graft survival and patient survival. The standard technique for lung preservation is still SCS in the vast majority of centres.

In lung transplantation there are two main systems that have been used for *ex situ* NMP. A number of devices, either fixed or portable, have been used in the clinical setting [106]. The Steen group (Lund, Sweden) described the first successful lung transplantation after *ex situ* NMP with six out of nine donor lungs that had initially been rejected for transplantation. The six recipients survived the first 3 months and four of the six were alive at 1 year [107]. After modification of Steen's initial *ex situ* NMP protocol, a matched controlled study from Toronto of 20 high-risk lungs preserved with *ex situ* NMP compared to conventional risk SCS lungs (n = 116) reported no statistically significant difference in the primary endpoint of primary graft dysfunction 72 h post-transplantation (15 % *v.* 30 %, p = 0.11); or secondary endpoints of 30-day mortality, bronchial complications, duration of mechanical ventilation, intensive care unit length of stay or hospital length of stay [108].

In a follow-up study, the *ex situ* NMP group (n = 50) was compared to an SCS group (n = 235) and the incidence of primary graft dysfunction grade 3 at 72 h was lower (2 % *v.* 9 %, p = 0.14) with similar 30-day mortality (4 % *v.* 3.5 %, p = 1.0), and 1-year survival (87 % *v.* 86 %, p = 1.0) [109]. In a further study from Toronto, patients transplanted with DCD lungs after *ex situ* NMP (n = 28) were compared to patients transplanted with DCD lungs after SCS (n = 27) and had similar patient survival (86 % *v.* 92 %, p = 0.68) but shorter hospital stay (median 18 *v.* 23 days, p = 0.047) and a shorter length of mechanical ventilation (2 *v.* 3 days, p = 0.059) [110]. In a retrospective UK study from Harefield, lungs initially deemed unusable for transplantation (n = 13) underwent *ex situ* NMP (adapting the Toronto protocol) and 46 % (n = 6) were transplanted with 100 % survival at 3 months [111]. The reported conversion rate from *ex situ* NMP to transplantation is lower in the Harefield experience at 46 % compared to the Swedish (67 %) and Toronto (87 %) experience [111]. In a combined analysis of UK, Sweden and Toronto experience, only two deaths within 90 days were reported in over 65 *ex situ* NMP lung transplants [112].

NMP was performed in lungs initially considered unsuitable for transplantation (n = 32) and compared to SCS controls (n = 81) with similar rates of primary graft dysfunction after 72 h (9.5 % *v.* 8.5 %, p = 1), 30-day mortality (3.3 % *v.* 3.7 %, p = 0.69) and 1-year survival (93 % *v.* 91 %, p = 0.8) [113]. In a single-centre RCT from Vienna standard criteria lungs were randomised to *ex situ* NMP (n = 39) or SCS (n = 41) with no significant difference in primary graft dysfunction (6 % *v.* 20 %, p = 0.10), need for post-operative prolonged extracorporeal membrane oxygenation (6 % *v.* 12 %, p = 0.44), 30-day survival (97 % *v.* 100 %, p = 0.46) or intubation time, intensive care stay and hospital stay. There was also loss of some standard criteria donor lungs due to technical issues during perfusion, making exposure of all donor lungs to *ex situ* NMP unattractive [114]. In the largest multicentre RCT (INSPIRE, NCT01630434) of EVNP (n = 151) compared to SCS (n = 169), a composite end-point of a 30-day patient survival (96 % *v.* 100 %) and the incidence of primary graft dysfunction of grade 3 within 72 h (18 % *v.* 30 %, p = 0·015) was not statistically significantly different between the groups (70 % *v.* 79 %, p = 0.068). Patient survival at 1-year post-transplant was also similar (89 % *v.* 88 %) [115].

DEVELOP-UK was a multicentre (n = 5) observational study that assessed *ex situ* NMP in extended criteria lungs (53 assessed and 18 transplanted) in comparison to standard donor lungs (n = 184). The study was terminated early due to higher rate of very early grade 3 primary graft dysfunction (44 % *v.* 18 %) and a need for unplanned extracorporeal membrane oxygenation support (39 % *v.* 3 %) at increased cost (approximately £35 000 higher) in the *ex situ* NMP group. Survival at 30 days was similar (94 % *v.* 97 %) but by 12 months of follow-up the hazard ratio for mortality in the *ex situ* NMP arm relative to the standard arm was 1.96 (95 % CI 0.83 to 4.67) [112]. The use of *ex situ* NMP in extended criteria donor lung transplantation is still under evaluation in the EXPAND I (NCT01963780) [116] and II lung trials (NCT03343535), with preliminary data suggesting good donor lung utilisation [106]. Overall clinical outcomes of *ex situ* NMP treated lungs appear equivalent to SCS despite the use of *ex situ* NMP for lungs not initially considered suitable for transplantation [117-121].

11.6. Conclusion

Organ procurement and preservation techniques have seen a significant evolution over the last decade and adapted to the ever changing profile of the donor. The technical evolution was supported by rapid technological development allowing better preservation and the ability to evaluate the quality and function of the donated organ prior to

transplantation. The evolution of organ preservation continues at a very fast pace and is likely to have the greatest impact in the coming years in terms of increasing organ utilisation and improving the function of the transplanted organs.

Research agenda

From the literature and discussion of the available evidence, several topics were identified for which evidence is inconsistent, insufficient or non-existent. For the benefit of patients undergoing transplant procedures, the authors of this guide recommend that future research, where possible in well-designed RCTs, should focus on these research gaps:

1 Define the role of *ex situ* machine perfusion and the optimal utilisation of perfusion technologies tailored to the individual donated organ
2 The role of single *v.* dual *in situ* cold perfusion in DCD donors
3 The benefit of *ante mortem* heparin administration and impact on organ utilisation and outcomes in DCD donors
4 The role of *en bloc* removal of liver and pancreas and impact on transplant function.

11.7. References

1. Englesbe MJ, Merion RM. The riskiest job in medicine: transplant surgeons and organ procurement travel. *Am J Transplant* 2009;9(10):2406-15.
2. Englesbe MJ, Shah S, Cutler JA *et al.* Improving organ procurement travel practices in the United States: proceedings from the Michigan Donor Travel Forum. *Am J Transplant* 2010;10(3):458-63.
3. Conway MB, Saunders R, Munn SR *et al.* Combined liver/pancreatico-duodenal procurement effect on allograft function. *Transplant Proc* 1990;22:429-30.
4. Starzl TE, Hakala TR, Shaw BW Jr *et al.* A flexible procedure for multiple cadaveric organ procurement. *Surg Gynecol Obstet* 1984;158:223-30.
5. de Ville de Goyet J, Hausleithner V, Malaise J *et al.* Liver procurement without *in situ* portal perfusion. A safe procedure for more flexible multiple organ harvesting. *Transplantation* 1994;57(9):1328-32.
6. Nghiem DD, Cottington EM. Pancreatic flush injury in combined pancreas–liver recovery. *Transpl Int* 1992;5:19-22.
7. Ramcharan T, Glessing B, Lake JR *et al.* Outcome of other organs recovered during *in situ* split-liver procurements. *Liver Transplant* 2001;7(10):853-7.
8. Feuillu B, Cormier L, Frimat L *et al.* Kidney cooling during multi-organ harvesting. Descriptive study. *Prog Urol* 2001;11(4):631-5.
9. Imagawa DK, Olthoff KM, Yersiz H *et al.* Rapid en bloc technique for pancreas–liver procurement. Improved early liver function. *Transplantation* 1996; 61(11):1605-9.
10. Watson CJ, Harper SJ. Anatomical variation and its management in transplantation. *Am J Transplant* 2015;15:1459-71.
11. Moench C, Moench K, Lohse AW *et al.* Prevention of ischemic-type biliary lesions by arterial back-table pressure perfusion. *Liver Transplant* 2003;9:285-9.
12. Tisone G, Orlando G, Pisani F *et al.* Gravity perfusion versus high-pressure perfusion in kidney transplantation: results from a prospective randomized study. *Transplant Proc* 1999;31:3386-7.
13. Tokunaga Y, Ozaki N, Wakashiro S *et al.* Effects of perfusion pressure during flushing on the viability of the procured liver using noninvasive fluorometry. *Transplantation* 1988;45:1031-5.
14. Suárez F, Otero A, Solla M *et al.* Biliary complications after liver transplantation from Maastricht category-2 non-heart-beating donors. *Transplantation* 2008; 85(1):9-14.
15. Quintela J, Gala B, Baamonde I *et al.* Long-term results for liver transplantation from non-heart-beating donors maintained with chest and abdominal compression–decompression. *Transplant Proc* 2005;37: 3857-8.
16. Reich DJ, Mulligan DC, Abt PL *et al.* ASTS recommended practice guidelines for controlled donation after cardiac death organ procurement and transplantation. *Am J Transplant* 2009;9:2004-11.
17. Bernat JL, D'Alessandro AM, Port FK *et al.* Report of a national conference on donation after cardiac death. *Am J Transplant* 2006;6:281-91.
18. Summers DM, Watson CJ, Pettigrew GJ *et al.* Kidney donation after circulatory death (DCD): state of the art. *Kidney Int* 2015;88:241-9.
19. Suntharalingam C, Sharples L, Dudley C *et al.* Time to cardiac death after withdrawal of life-sustaining treatment in potential organ donors. *Am J Transplant* 2009;9:2157-65.
20. Casavilla A, Ramirez C, Shapiro R *et al.* Experience with liver and kidney allografts from non-heart-beating donors. *Transplantation* 1995;59:197-203.
21. Moench C, Heimann A, Foltys D *et al.* Flow and pressure during liver preservation under *ex situ* and *in situ* perfusion with University of Wisconsin solution and histidine–tryptophan–ketoglutarate solution. *Eur Surg Res* 2007;39:175-81.
22. Van Raemdonck D, Keshavjee S, Levvey B *et al.* Donation after circulatory death in lung transplantation – five-year follow-up from International Society for Heart and Lung Transplantation registry. *J Heart Lung Transplant* 2019 Dec;38(12):1235-45.
23. Dhital KK, Iyer A, Connellan M *et al.* Adult heart transplantation with distant procurement and ex-vivo

preservation of donor hearts after circulatory death: a case series. *Lancet* 2015;385:2585-91.

24. Hessheimer AJ, Coll E, Torres F *et. al.* Normothermic regional perfusion vs. super-rapid recovery in controlled donation after circulatory death liver transplantation. *J Hepatol* 2019 Apr;70(4):658-65.
25. Oniscu GC, Randle LV, Muiesan P *et al.* In situ normothermic regional perfusion for controlled donation after circulatory death – the United Kingdom experience. *Am J Transplant* 2014;14:2846-54.
26. Watson CJE, Hunt F, Messer S *et al.* In situ normothermic perfusion of livers in controlled circulatory death donation may prevent ischemic cholangiopathy and improve graft survival. *Am J Transplant* 2019 Jun; 19(6):1745-58.
27. Magliocca JF, Magee JC, Rowe SA *et al.* Extracorporeal support for organ donation after cardiac death effectively expands the donor pool. *J Trauma* 2005; 58(6):1095-1101;discussion 1101-2.
28. Rojas-Peña A, Sall LE, Gravel MT *et al.* Donation after circulatory determination of death: the University of Michigan experience with extracorporeal support. *Transplantation* 2014;98:328-34.
29. De Carlis R, Di Sandro S, Lauterio A *et al.* Liver grafts from donors after circulatory death on regional perfusion with extended warm ischemia compared with donors after brain death. *Liver Transplant* 2018;24(11): 1523-35.
30. Butler AJ, Randle LV, Watson CJ. Normothermic regional perfusion for donation after circulatory death without prior heparinization. *Transplantation* 2014; 97(12):1272-8.
31. Minambres E, Suberviola B, Dominguez-Gil B *et al.* Improving the outcomes of organs obtained from controlled donation after circulatory death donors using abdominal normothermic regional perfusion. *Am J Transplant* 2017;17(8):2165-72.
32. Antoine C, Videcoq M, Riou B *et al.* Controlled donation after circulatory death (cDCD) donors may become similar to brain death donors (DBD). *Am J Transplant* 2017;17(suppl 3).
33. De Carlis L, De Carlis R, Muiesan P. Past, present, and future of donation after circulatory death in Italy. *Updates Surg* 2019;71(1):7-9.
34. Ravaioli M, De Pace V, Comai G *et al.* Preliminary experience of sequential use of normothermic and hypothermic oxygenated perfusion for donation after circulatory death kidney with warm ischemia time over the conventional criteria – a retrospective and observational study. *Transpl Int* 2018;31(11):1233-44.
35. Lomero M, Gardiner D, Coll E *et al.* Donation after circulatory death today: an updated overview of the European landscape. *Transpl Int* 2020;33(1):76-88.
36. ONT (Organización Nacional de Trasplantes), *Donación en asistolia en España: situación actual y recomendaciones* ['Donation after circulatory death in Spain: current situation and recommendations']. National consensus document 2012 (in Spanish), available at www.ont.es/infesp/DocumentosDeConsenso/DONACIÓN%20EN%20ASISTOLIA%20EN%20ESPAÑA.%20SITUACIÓN%20ACTUAL%20Y%20RECOMENDACIONES.pdf, accessed 21 Jun 2021.
37. Oniscu GC, Siddique A, Dark J. Dual temperature multi-organ recovery from a Maastricht category III donor after circulatory death. *Am J Transplant* 2014; 14:2181-6.
38. Miñambres E, Rubio JJ, Coll E, Domínguez-Gil B. Donation after circulatory death and its expansion in Spain. *Curr Opin Organ Transplant* 2018;23:120-29.
39. Miñambres E, Ruiz P, Ballesteros MA *et al.* Combined lung and liver procurement in controlled donation after circulatory death using normothermic abdominal perfusion. Initial experience in two Spanish centers. *Am J Transplant* 2020;20:231-40.
40. Tchana-Sato V, Ledoux D, Detry O *et al.* Successful clinical transplantation of hearts donated after circulatory death using normothermic regional perfusion. *J Heart Lung Transplant*. 2019 Jun;38(6):593-8.
41. Tchana-Sato V, Ledoux D, Vandendriessche K *et al.* First report of a successful pediatric heart transplantation from donation after circulatory death with distant procurement using normothermic regional perfusion and cold storage. *J Heart Lung Transplant*. 2019 Oct;38(10):1112-15.
42. Manara A, Shemie SD, Large S *et al.* Maintaining the permanence principle for death during *in situ* normothermic regional perfusion for donation after circulatory death organ recovery: a United Kingdom and Canadian proposal. *Am J Transplant*. 2020 Jan 10. DOI:10.1111/ajt.15775.
43. Messer S, Page A, Axell R *et al.* Outcome after heart transplantation from donation after circulatory-determined death donors. *J Heart Lung Transplant* 2017; 36(12):1311-18.
44. Page A, Messer S, Large SR. Heart transplantation from donation after circulatory determined death. *Ann Cardiothorac Surg* 2018;7(1):75-81.
45. Messer S, Page A, Colah S *et al.* Human heart transplantation from donation after circulatory-determined death donors using normothermic regional perfusion and cold storage. *J Heart Lung Transplant*. 2018 Jul;37(7):865-9.
46. Gámez P, Díaz-Hellin V, Marrón C *et al.* Development of a non-heart-beating lung donor program with 'bithermia preservation', and results after one year of clinical experience. *Arch Bronconeumol* 2012;48(9): 338-41.
47. Southard JH. The right solution for organ preservation.

Business Briefing, *North American Pharmacotherapy* 2004;2:10.

48. Parsons RF, Guarrera JV. Preservation solutions for static cold storage of abdominal allografts: which is best? *Curr Opin Organ Transplant* 2014;19(2):100-7.
49. Timsit MO, Tullius SG. Hypothermic kidney preservation: a remembrance of the past in the future? *Curr Opin Organ Transplant* 2011;16:162-8.
50. O'Callaghan JM, Knight SR, Morgan RD *et al.* Preservation solutions for static cold storage of kidney allografts: a systematic review and meta-analysis. *Am J Transplant* 2012;12:896-906.
51. Fondevila C, Hessheimer AJ, Flores E *et al.* Applicability and results of Maastricht type 2 donation after cardiac death liver transplantation. *Am J Transplant* 2012;12:162-70.
52. British Transplantation Society. United Kingdom guidelines: Transplantation from donors after deceased circulatory death, 2013; available at https://bts.org.uk/guidelines-standards/ , accessed: 21 Jun 2021.
53. O'Neill S, Srinivasa S, Callaghan CJ *et al.* Novel organ perfusion and preservation strategies in transplantation – where are we going in the UK? *Transplantation* 2020 Sep;104(9):1813-24. https://doi.org/10.1097/TP.0000000000003106.
54. Karangwa SA, Dutkowski P, Fontes P *et al.* Machine perfusion of donor livers for transplantation: a proposal for standardized nomenclature and reporting guidelines. *Am J Transplant* 2016;16(10):2932-42.
55. Jochmans I, Akhtar MZ, Nasralla D *et al.* Past, present, and future of dynamic kidney and liver preservation and resuscitation. *Am J Transplant* 2016;16(9):2545-55.
56. Abramowicz D, Oberbauer R, Heemann U *et al.* Recent advances in kidney transplantation: a viewpoint from the Descartes advisory board. *Nephrol Dial Transplant* 2018;33(10):1699-1707.
57. Moers C, Smits JM, Maathuis MH *et al.* Machine perfusion or cold storage in deceased-donor kidney transplantation. *N Engl J Med* 2009;360(1):7-19.
58. Jiao B, Liu S, Liu H *et al.* Hypothermic machine perfusion reduces delayed graft function and improves one-year graft survival of kidneys from expanded criteria donors: a meta-analysis. *PLoS One* 2013;8(12):e81826.
59. Deng R, Gu G, Wang D *et al.* Machine perfusion versus cold storage of kidneys derived from donation after cardiac death: a meta-analysis. *PLoS One* 2013;8(3):e56368.
60. Bathini V, McGregor T, McAlister VC *et al.* Renal perfusion pump vs cold storage for donation after cardiac death kidneys: a systematic review. *J Urol* 2013;189(6):2214-20.
61. O'Callaghan JM, Morgan RD, Knight SR *et al.* Systematic review and meta-analysis of hypothermic machine perfusion versus static cold storage of kidney allografts on transplant outcomes. *Br J Surg* 2013;100(8):991-1001.
62. Lam VW, Laurence JM, Richardson AJ *et al.* Hypothermic machine perfusion in deceased donor kidney transplantation: a systematic review. *J Surg Res* 2013;180(1):176-82.
63. Martinez Arcos L, Fabuel Alcaniz JJ, Gomez Dos Santos V, Burgos Revilla FJ. Functional results of renal preservation in hypothermic pulsatile machine perfusion versus cold preservation: systematic review and meta-analysis of clinical trials. *Transplant Proc* 2018;50(1):24-32.
64. Tingle SJ, Figueiredo RS, Moir JA *et al.* Machine perfusion preservation versus static cold storage for deceased donor kidney transplantation. *Cochrane Database Syst Rev* 2019;3:Cd011671.
65. Peng P, Ding Z, He Y *et al.* Hypothermic machine perfusion versus static cold storage in deceased donor kidney transplantation: a systematic review and meta-analysis of randomized controlled trials. *Artif Organs* 2019 May;43(5):478-89. DOI:10.1111/aor.13364.
66. Jochmans I, Moers C, Smits JM *et al.* Machine perfusion versus cold storage for the preservation of kidneys donated after cardiac death: a multicenter, randomized, controlled trial. *Ann Surg* 2010;252(5):756-64.
67. Treckmann J, Moers C, Smits JM *et al.* Machine perfusion versus cold storage for preservation of kidneys from expanded criteria donors after brain death. *Transpl Int* 2011;24(6):548-54.
68. Watson CJ, Wells AC, Roberts RJ *et al.* Cold machine perfusion versus static cold storage of kidneys donated after cardiac death: a UK multicenter randomized controlled trial. *Am J Transplant* 2010;10(9):1991-9.
69. Jochmans I, Moers C, Ploeg R, Pirenne J. To perfuse or not to perfuse kidneys donated after cardiac death. *Am J Transplant* 2011;11(2):409-10.
70. Patel K, Nath J, Hodson J *et al.* Outcomes of donation after circulatory death kidneys undergoing hypothermic machine perfusion following static cold storage: a UK population-based cohort study. *Am J Transplant* 2018;18(6):1408-14.
71. Bellini MI, Charalampidis S, Herbert PE *et al.* Cold pulsatile machine perfusion versus static cold storage in kidney transplantation: a single centre experience. *BioMed Research International* 2019;2019:7435248.
72. Gallinat A, Amrillaeva V, Hoyer DP *et al.* Reconditioning by end-ischemic hypothermic in-house machine perfusion: a promising strategy to improve outcome in expanded criteria donors kidney transplantation. *Clin Transplant* 2017;31(3). https://doi.org/10.1111/ctr.12904.
73. Jochmans I, Hofker H, Davies L *et al.* Oxygenated

hypothermic machine perfusion of kidneys donated after circulatory death: an international randomised controlled trial. *Am J Transplant* 2019;19(suppl 3).

74. Nicholson ML, Hosgood SA. Renal transplantation after *ex vivo* normothermic perfusion: the first clinical study. *Am J Transplant* 2013;13(5):1246-52.
75. Hosgood SA, Thompson E, Moore T *et al.* Normothermic machine perfusion for the assessment and transplantation of declined human kidneys from donation after circulatory death donors. *Br J Surg* 2018; 105(4):388-94.
76. Chandak P, Phillips BL, Uwechue R *et al.* Dissemination of a novel organ perfusion technique: *ex vivo* normothermic perfusion of deceased donor kidneys. *Artif Organs* 2019 Nov;43(11):e308-19.
77. Rijkse E, de Jonge J, Kimenai HJAN *et al.* Safety and feasibility of 2 h of normothermic machine perfusion of donor kidneys in the Eurotransplant Senior Program. *BJS Open* 2021 Jan;5(1). DOI:10.1093/bjsopen/zraa024.
78. Hosgood SA, Saeb-Parsy K, Wilson C *et al.* Protocol of a randomised controlled, open-label trial of *ex vivo* normothermic perfusion versus static cold storage in donation after circulatory death renal transplantation. *BMJ Open* 2017;7(1):e012237.
79. Guarrera JV, Henry SD, Samstein B *et al.* Hypothermic machine preservation in human liver transplantation: the first clinical series. *Am J Transplant* 2010;10(2): 372-81.
80. Guarrera JV, Henry SD, Samstein B *et al.* Hypothermic machine preservation facilitates successful transplantation of 'orphan' extended criteria donor livers. *Am J Transplant* 2015;15(1):161-9.
81. van Rijn R, Karimian N, Matton APM *et al.* Dual hypothermic oxygenated machine perfusion in liver transplants donated after circulatory death. *Br J Surg* 2017;104(7):907-17.
82. Dutkowski P, Polak WG, Muiesan P *et al.* First comparison of hypothermic oxygenated perfusion versus static cold storage of human donation after cardiac death liver transplants: an international-matched case analysis. *Ann Surg* 2015;262(5):764-70; discussion 770-1.
83. Schlegel A, Muller X, Kalisvaart M *et al.* Outcomes of DCD liver transplantation using organs treated by hypothermic oxygenated perfusion before implantation. *J Hepatol* 2019;70(1):50-57.
84. Treckmann J, Minor T, Saad S *et al.* Retrograde oxygen persufflation preservation of human livers: a pilot study. *Liver Transpl* 2008;14(3):358-64.
85. Mergental H, Perera MTPR, Laing RW *et al.* Transplantation of declined liver allografts following normothermic ex-situ evaluation. *Am J Transplant* 2016;16(11):3235-45.
86. Selzner M, Goldaracena N, Echeverri J *et al* Normothermic *ex vivo* liver perfusion using steen solution as perfusate for human liver transplantation: first North American results. *Liver Transpl* 2016;22(11):1501-8.
87. Ravikumar R, Jassem W, Mergental H *et al.* Liver transplantation after *ex vivo* normothermic machine preservation: a phase 1 (first-in-man) clinical trial. *Am J Transplant* 2016;16(6):1779-87.
88. Angelico R, Perera MT, Ravikumar R *et al.* Normothermic machine perfusion of deceased donor liver grafts is associated with improved postreperfusion hemodynamics. *Transplantation Direct* 2016;2(9):e97.
89. Nasralla D, Coussios CC, Mergental H *et al.* A randomized trial of normothermic preservation in liver transplantation. *Nature* 2018;557(7703):50-56.
90. Watson CJE, Kosmoliaptsis V, Pley C *et al.* Observations on the *ex situ* perfusion of livers for transplantation. *Am J Transplant* 2018;18(8):2005-20.
91. Watson CJE, Kosmoliaptsis V, Randle LV *et al.* Normothermic perfusion in the assessment and preservation of declined livers before transplantation: hyperoxia and vasoplegia – important lessons from the first 12 cases. *Transplantation* 2017;101(5):1084-98.
92. Hoyer DP, Mathe Z, Gallinat A *et al.* Controlled oxygenated rewarming of cold stored livers prior to transplantation: first clinical application of a new concept. *Transplantation* 2016;100(1):147-52.
93. de Vries Y, Matton APM, Nijsten MWN *et al.* Pretransplant sequential hypo- and normothermic machine perfusion of suboptimal livers donated after circulatory death using a hemoglobin-based oxygen carrier perfusion solution. *Am J Transplant* 2019;19(4): 1202-11.
94. Dholakia S, Royston E, Sharples EJ *et al.* Preserving and perfusing the allograft pancreas: past, present, and future. *Transplant Rev (Orlando)* 2018;32(3):127-31.
95. Leemkuil M, Lier G, Engelse MA *et al.* Hypothermic oxygenated machine perfusion of the human donor pancreas. *Transplantation Direct* 2018;4(10):e388.
96. Hamaoui K, Gowers S, Sandhu B *et al.* Development of pancreatic machine perfusion: translational steps from porcine to human models. *J Surg Res* 2018;223: 263-74.
97. Branchereau J, Renaudin K, Kervella D *et al.* Hypothermic pulsatile perfusion of human pancreas: preliminary technical feasibility study based on histology. *Cryobiology* 2018;85:56-62.
98. Kelly AC, Smith KE, Purvis WG *et al.* Oxygen perfusion (persufflation) of human pancreata enhances insulin secretion and attenuates islet proinflammatory signaling. *Transplantation* 2019;103(1):160-67.
99. Barlow AD, Hamed MO, Mallon DH *et al.* Use of *ex vivo* normothermic perfusion for quality assessment

of discarded human donor pancreases. *Am J Transplant* 2015;15(9):2475-82.

100. Steen S, Paskevicius A, Liao Q, Sjoberg T. Safe orthotopic transplantation of hearts harvested 24 hours after brain death and preserved for 24 hours. *Scand Cardiovasc J* 2016;50(3):193-200.

101. Ardehali A, Esmailian F, Deng M *et al.* Ex-vivo perfusion of donor hearts for human heart transplantation (PROCEED II): a prospective, open-label, multicentre, randomised non-inferiority trial. *Lancet* 2015; 385(9987):2577-84.

102. Garcia Saez D, Zych B, Sabashnikov A *et al.* Evaluation of the organ care system in heart transplantation with an adverse donor/recipient profile. *Ann Thorac Surg* 2014;98(6):2099-2105; discussion 2105-6.

103. White CW, Messer SJ, Large SR *et al.* Transplantation of hearts donated after circulatory death. *Front Cardiovasc Med* 2018;5:8.

104. Hessheimer AJ, Gastaca M, Miñambres E *et al.* representing the SETH Working Group on DCD Donation after Circulatory Death Liver Transplantation: Consensus Statements from the Spanish Liver Transplantation Society. *Transpl Int* 2020 Apr 20. DOI: 10.1111/tri.13619. Online ahead of print.

105. Garcia Saez D, Bowles CT, Mohite PN *et al.* Heart transplantation after donor circulatory death in patients bridged to transplant with implantable left ventricular assist devices. *J Heart Lung Transplant* 2016;35(10):1255-60.

106. Loor G. EVLP: Ready for prime time? *Semin Thorac Cardiovasc Surg* 2019;31(1):1-6.

107. Ingemansson R, Eyjolfsson A, Mared L *et al.* Clinical transplantation of initially rejected donor lungs after reconditioning *ex vivo*. *Ann Thorac Surg* 2009;87(1): 255-60.

108. Cypel M, Yeung JC, Liu M *et al.* Normothermic *ex vivo* lung perfusion in clinical lung transplantation. *N Engl J Med* 2011;364(15):1431-40.

109. Cypel M, Yeung JC, Machuca T *et al.* Experience with the first 50 *ex vivo* lung perfusions in clinical transplantation. *J Thorac Cardiovasc Surg* 2012;144(5): 1200-06.

110. Machuca TN, Mercier O, Collaud S *et al.* Lung transplantation with donation after circulatory determination of death donors and the impact of *ex vivo* lung perfusion. *Am J Transplant* 2015;15(4):993-1002.

111. Zych B, Popov AF, Stavri G *et al.* Early outcomes of bilateral sequential single lung transplantation after ex-vivo lung evaluation and reconditioning. *J Heart Lung Transplant* 2012;31(3):274-81.

112. Fisher A, Andreasson A, Chrysos A *et al.* An observational study of donor *ex vivo* lung perfusion in UK lung transplantation: DEVELOP-UK. *Health Technol Assess* 2016 Nov;20(85):1-276. DOI:10.3310/hta20850.

113. Sage E, Mussot S, Trebbia G *et al.* Lung transplantation from initially rejected donors after *ex vivo* lung reconditioning: the French experience. *Eur J Cardiothorac Surg* 2014;46(5):794-9.

114. Slama A, Schillab L, Barta M *et al.* Standard donor lung procurement with normothermic *ex vivo* lung perfusion: a prospective randomized clinical trial. *J Heart Lung Transplant* 2017;36(7):744-53.

115. Warnecke G, Van Raemdonck D, Smith MA *et al.* Normothermic ex-vivo preservation with the portable Organ Care System lung device for bilateral lung transplantation (INSPIRE): a randomised, open-label, non-inferiority, phase 3 study. *Lancet Respir Med* 2018; 6(5):357-67.

116. Loor G, Warnecke G, Villavicencio MA *et al.* Portable normothermic ex-vivo lung perfusion, ventilation, and functional assessment with the Organ Care System on donor lung use for transplantation from extended-criteria donors (EXPAND): a single-arm, pivotal trial. *Lancet Respir Med* 2019 Nov;7(11):975-84.

117. Aigner C, Slama A, Hotzenecker K *et al.* Clinical *ex vivo* lung perfusionpushing the limits. *Am J Transplant* 2012;12(7):1839-47.

118. Wallinder A, Ricksten SE, Silverborn M *et al.* Early results in transplantation of initially rejected donor lungs after *ex vivo* lung perfusion: a case-control study. *Eur J Cardiothorac Surg* 2014;45(1):40-4; discussion 44-5.

119. Wallinder A, Riise GC, Ricksten SE *et al.* Transplantation after *ex vivo* lung perfusion: A midterm follow-up. *J Heart Lung Transplant* 2016;35(11):1303-10.

120. Zhang ZL, van Suylen V, van Zanden JE *et al.* First experience with *ex vivo* lung perfusion for initially discarded donor lungs in the Netherlands: a single-centre study. *Eur J Cardiothorac Surg* 2019;55(5): 920-6.

121. Nilsson T, Wallinder A, Henriksen I *et al.* Lung transplantation after *ex vivo* lung perfusion in two Scandinavian centres. *Eur J Cardiothorac Surg* 2019; 55(4):766-72.

Related material

Appendix 19 Antibiotic prophylaxis in deceased organ donors
Appendix 20 *En bloc* liver–pancreas removal in deceased brain-dead donors
Appendix 21 *Ante mortem* heparin in DCD donors
Appendix 22 Single *v.* dual *in situ* cold perfusion in DCD donors

Chapter 12. Donation after the circulatory determination of death (DCD)

12.1. Introduction

The majority of transplants from deceased organ donors use organs recovered from patients whose death has been declared on the basis of the irreversible cessation of neurological functions, i.e. donation after brain death (DBD). However, the shortage of organs for transplantation, along with technical developments leading to improved post-transplant outcomes, has resulted in increasing interest in donation from persons whose death has been determined by circulatory criteria, i.e. donation after the circulatory determination of death (DCD).

The first attempt to classify DCD donors dates back to 1995, when the first International Workshop on what was then called 'non-heart-beating donation' took place in Maastricht (Netherlands) [1]. DCD donors were classified in one of four categories, depending on the circumstances of the cardiac arrest (CA) preceding death. The Maastricht classification was updated at a dedicated conference held in Paris (France) in February 2013 (Table 12.1) and now includes the following categories [2]:

1. Category I: Donation from persons who have suffered a CA and in whom cardiopulmonary resuscitation (CPR) has not been attempted for various reasons. This is nowadays only compatible with tissue donation.
2. Category II: Donation from persons who have been declared dead following an unexpected CA and in whom CPR has been exhausted and deemed unsuccessful by the attending team. This type of donation includes two subcategories:

i. Category IIa: The CA has occurred out of hospital. The moment of loss of consciousness, or that of loss of pulse, has been documented and the duration of the CA can be estimated. Emergency services have attempted to resuscitate the patient, but according to international standards (American Heart Association, European Resuscitation Council and International Liaison Committee on Resuscitation [3-5]), CA has been deemed irreversible.
ii. Category IIb: The CA has occurred in a hospitalised patient (e.g. emergency room, hospital ward), with otherwise similar settings to category IIa. Organ donation is often unlikely due to the patient's advanced age and/or comorbidities.

3. Category III: Donation from patients in whom CA is expected to occur following the planned withdrawal of life-sustaining therapy (WLST) because this is no longer in the best interests of the critically ill patient.
4. Category IV: Donation from patients who meet brain death criteria and have suffered a CA. In the original Maastricht classification, this category referred to unrecovered CA derived from the haemodynamic instability inherent to the brain death condition, which still allowed

the activation of a DCD procedure. This is a rare type of donation, because adequate intensive care treatment is usually able to prevent such events (see Chapter 5). However, category IV also refers to donation after a CA that follows a planned withdrawal of mechanical ventilation and organ support in a patient who has been diagnosed as brain dead but where the DBD pathway cannot proceed for a variety of reasons (e.g. when the family wishes to be with the donor at the time of the cessation of the heartbeat or in countries where DBD is culturally difficult to accept).

Categories II and III are the most common types of DCD. Because in Category II the CA causing the death of the individual occurs in a non-monitored setting, this chapter uses the term 'uncontrolled DCD' (uDCD) to refer to donation from persons declared dead following unsuccessful CPR. Similarly, since in Category III the CA is anticipated and occurs in controlled and monitored circumstances, the term 'controlled DCD' (cDCD) is used to refer to donation from persons declared dead following the planned WLST. Category IV DCD is practised mainly in China in cases where the patient is confirmed brain dead and the withdrawal of ongoing organ support is undertaken in a planned fashion.

Finally, cDCD can also follow euthanasia (known in Canada as medical assistance in dying, MAID) in countries where such practices are legal and, for the purposes of this chapter, is classified as Category V DCD.

Note that cDCD and uDCD donors can also be classified as possible, potential, eligible, actual or utilised DCD donors, depending on the stage of the process of donation, as specified in Chapter 2 (see §2.3).

Although DCD now represents 20 % of deceased donors reported globally [6] it is so far practised in only a minority of countries [7, 8]. Legal and ethical issues, lack of technical expertise or organisational capability, and a lack of professional confidence in the outcome of transplantation with organs obtained from DCD donors [7] are the main obstacles that preclude the development of DCD programmes in other jurisdictions. The implementation of DCD is increasing in Europe. Today, 12 European countries have cDCD and 14 countries uDCD programmes, the two types co-existing in eight countries [7] (Table 12.2). The fact that countries have focused on one specific type of DCD may be related to different legislations, ethical concerns, end-of-life practices (with WLST based on futility being a limited practice in some settings) and organisational approaches to the treatment of out-of-hospital CA.

In Belgium, Canada and the Netherlands, cDCD is also possible after euthanasia (known as MAID in Canada). Other parts of the world are also planning to introduce legislation to allow this practice. This needs to take place in a hospital and a thorough evaluation of the motives for euthanasia and MAID must take place according to national protocols or guidance [9-11]. Countries engaging in these activities need to discuss various legal and logistical issues, such as the hospital admission of the patient, identifying the doctor responsible for the individual, and how and by whom death is determined, among others.

Realising the full potential of DCD can make significant contributions to further expanding the deceased organ donor pool [12]. DCD must be

Table 12.1. **Maastricht classification of DCD donors, as modified in Paris (February 2013), with new Category V (added for this chapter)**

Maastricht Category and type of DCD	Observations
I: Found dead (uncontrolled) I a out of hospital I b in hospital	Sudden unexpected cardiac arrest, with no attempt at resuscitation by a medical team.
II: Witnessed cardiac arrest (uncontrolled) II a out of hospital II b in hospital	Sudden unexpected irreversible cardiac arrest, with unsuccessful attempt at resuscitation by a medical team
III: Withdrawal of life-sustaining therapy* (controlled DCD)	Planned, expected cardiac arrest, following the withdrawal of life-sustaining therapy
IV: Cardiac arrest while brain dead (uncontrolled or controlled)	Sudden or planned cardiac arrest after brain death diagnosis process, but before organ recovery
V: Cardiac arrest after euthanasia†	Anticipated cardiac arrest following euthanasia or medically assisted dying

* This category mainly refers to the decision to withdraw life-sustaining therapies.

† This is not a Maastricht category, but legislation in some countries allows euthanasia. Death is anticipated but, unlike Category III, death does not follow WLST and this is therefore classified as an additional category (Category V).

grounded on a robust regulatory framework. Legislation enabling this activity should be issued. National protocols or guidelines should be available, and a continuous evaluation of activities and results should be undertaken by health authorities. All European countries currently practising DCD have legal and/or professional guidance regulating the practice of DCD [7]

This chapter provides an overview of the process of uDCD and cDCD, highlighting factors for success at each step of the different processes, provided that this activity is possible within a given jurisdiction.

12.2. Uncontrolled donation after circulatory determination of death

UDCD refers to donation from persons whose death has occurred following an unexpected CA and who have not been successfully resuscitated. Although this type of donation can substantially increase the potential donor pool [13], uDCD is practised in only a few countries which have been able to overcome the different legal, ethical and logistical obstacles related to this type of donation [14]. France, Russia and Spain have the largest experience with uDCD [7].

Good long-term kidney graft survival has been reported from uDCD procedures, although an increased incidence of delayed graft function (DGF) and early graft failure have been described in comparison with ideal DBD kidneys [15-20]. These results can be improved by the use of *in situ* normothermic regional perfusion (NRP) [19-21]. The role of *ex situ* machine perfusion is still to be elucidated [22-24]. The most recent data suggest that patients who receive DCD donor kidneys show better post-transplant outcomes with grafts obtained from cDCD in comparison to uDCD donors [7].

Although the use of NRP has also led to promising results in liver transplantation from uDCD donors, these results are still mixed and not consistently similar to the results of livers from DBD donors, mainly due to a higher incidence of primary graft dysfunction, non-function and biliary complications [25-33]; uDCD liver transplantation has also been associated with severe haemodynamic and coagulation abnormalities requiring a proactive recipient-management strategy to avoid catastrophic consequences [34]. There is still limited experience in uDCD lung transplantation; however, the reported results are encouraging [35-40].

Category IIa uDCD donors can yield good-quality organs when strict selection criteria are applied; uDCD donors may have been individuals with a healthy lifestyle until their sudden death. They have a low risk of nosocomial infection because they have not been previously admitted into an intensive care unit (ICU). Importantly, uDCD donors have not been exposed to the systemic organ injury caused by brain death (see Chapter 5). Counterbalancing these positive considerations, organs from uDCD donors are subject to the damaging effect of warm ischaemia. There is also the risk of being unable to obtain a detailed medical history within the short time frame provided by uDCD procedures. The process of donation in this setting should be designed not only to minimise the duration of warm ischaemia and its impact on organ viability, but also to ensure the highest possible safety of the donated organs [41].

The key steps in the process of uDCD, particularly of category IIa, are represented in Figure 12.1, and summarised in the rest of this section (§12.2) below [15]. Technically, the IIb process is identical to the IIa process, except for the absence of an out-of-hospital stage and the step of donor transfer. The complementary Figure 12.2 outlines the limits of warm ischaemia time (WIT) and cold ischaemia time (CIT).

12.2.1. Identification and referral of potential donors

There must be no perception of a conflict of interest between decisions to stop CPR or to apply advanced resuscitation techniques of life support such as extracorporeal cardiopulmonary resuscitation (ECLS), also known as extracorporeal membrane oxygenation, where available, and consideration of the suitability of the patient as a potential uDCD donor [42]. Programmes that integrate ECLS and uDCD help to formalise the pathway to uDCD referral in patients who are not eligible for ECLS [43].

Potential uDCD donors are persons with a documented CA in whom advanced CPR has been exhausted in accordance with international standards and deemed unsuccessful by the attending team – this will also include novel advanced CPR techniques if these are components of specific local CPR protocols [3-5, 42]. Potential donors should be medically suitable on the basis of similar criteria to those applied in DBD. In addition, some specific selection criteria need to be met (see Table 12.3) and there are limitations to the time interval between CA and the initiation of *in situ* preservation strategies, traditionally referred to as duration of total WIT (see Figure 12.2).

Table 12.2. **Donation and transplant activity in Europe, 2008-16 [7]**

	DCD donors (n) 2008-2016		DCD donors (n) 2008-2016	% DCD donors over total deceased donors 2008-2016	Transplants from DCD donors (n) 2008-2016*					
	uDCD	cDCD			Kidney	Liver	Lung	Pancreas	Heart	Total
Austria	14	20	34	1.9 %	63	5	4	0	0	72
Belgium	16	633	649	23.7 %	870	440	326	37	0	1 673
Czech Republic	0	23	23	1.2 %	40	1	0	0	0	41
France	457	62	519	3.5 %	716	48	0	0	0	764
Ireland	—	21	21	3.0 %	42	0	3	0	0	45
Israel	8	—	8	1.2 %	11	0	0	0	0	11
Italy	29	9	38	0.3 %	45	14	4	0	0	63
Latvia	115	—	115	37.6 %	71	0	0	0	0	71
Lithuania	2	—	2	0.5 %	3	0	0	0	0	3
Netherlands	47	1 048	1 095	49.1 %	1 785	336	418	29	0	2 568
Norway	—	10	10	1.0 %	18	4	0	0	0	22
Poland	10	—	10	0.2 %	18	0	0	0	0	18
Portugal	10	—	10	0.4 %	12	0	0	0	0	12
Russia	1 280	0	1 280	32.1 %	2 171	0	0	0	0	2 171
Spain	997	757	1 754	11.5 %	2 348	339	164	3	0	2 854
Switzerland	1	70	71	7.3 %	96	45	21	3	0	165
United Kingdom	3	4 060	4 063	39.1 %	6 630	1 268	441	401	32	8 772
Total	**2 989**	**6 713**	**9 702**	**12.7 %**	**14 939**	**2 500**	**1 381**	**473**	**32**	**19 325**

*Transplants performed with organs obtained from DCD donors within the country.

cDCD: Controlled donation after circulatory death; DCD: Donation after circulatory death; uDCD: uncontrolled donation after circulatory death

Table 12.3. **Standard selection criteria for uDCD donors**

Advanced CPR started within a maximum of 15 min of the witnessed loss of consciousness or cardiac arrest (some programmes accept a maximum of 30 min for kidney donation).
Age between 18 and 60 years (some programmes accept donation from donors outside this age range).
Cause of death known (or suspected). Potential donors who die in circumstances that may interfere with judicial investigations should still be considered after consultation and agreement of the competent judicial authority.
No exsanguinating lesions from chest or abdominal wounds.
Normal external appearance (e.g. persons with signs of high-risk practices such as parenteral drug addiction should not usually be selected as potential donors).
Time between cardiac arrest and start of *in situ* preservation should be less than 150 min.

CPR: Cardio-pulmonary resuscitation.

When an individual suddenly suffers a CA on the street or at home, the sequence of events – after alerting the emergency services – should be as follows:

a. CA is assessed, and advanced CPR measures are initiated with the sole objective of saving the patient's life.

b. The time of CA is recorded according to the reports of witnesses.

c. If by at least 30 min after the initiation of advanced CPR measures in a non-hypothermic patient, attempts to achieve restoration of spontaneous circulation fail (according to the current American Heart Association, European Resuscitation Council and International Liaison Committee on Resuscitation guidelines and national/regional legislation), then resuscitation attempts can be considered unsuccessful and the individual can then be assessed as a potential uDCD donor based on the general and specific selection criteria for uDCD detailed in Table 12.3.

d. In some countries (e.g. Spain and France), patients whose out-of-hospital CA was followed by an unsuccessful attempt at resuscitation can be transferred to the hospital with the purpose of enabling organ donation. Both countries have active physician-led emergency medical services, and the potential of uDCD can be considered once advanced CPR has been declared

unsuccessful in the out-of-hospital setting and the patient does not meet criteria for an ECLS protocol (where available). The patient is then kept mechanically ventilated and external cardiac compression continues, but without further drug administration, since advanced CPR for resuscitative purposes has been exhausted. The team in charge of advanced CPR contacts the receiving hospital to provide information about the potential donor transfer and activation of the uDCD procedure. The hospital is informed about the estimated time of arrival. The hospital staff prepare to receive the potential donor. Simultaneously, the surgical team starts to prepare for the initiation of *in situ* preservation measures.

e. In other programmes (e.g. in the Netherlands), with paramedic-led emergency medical services, the possibility of uDCD in the setting of an irreversible CA is considered exclusively when such irreversibility has been determined in the in-hospital setting, limiting the activations to patients with a CA who are transferred to the hospital in anticipation of a therapeutic intervention. However, the sequence of events described above does not vary substantially.

For further information on the identification of uDCD donors, see Chapter 2.

12.2.2. Donor transfer

The transfer to hospital of a person with an irreversible CA for the purpose of considering organ donation should be carried out by the emergency medical services. Transfer of the potential uDCD donor is performed in an intensive care mobile unit maintaining the lines, but with no drug administration (no vaso-active drugs, no adrenaline, no anti-arrhythmics). As soon as the irreversibility of the CA under current international resuscitation guidelines has been declared, and if ECLS is not indicated where protocols are implemented, any kind of life support is considered futile. Cardiac compression and mechanical ventilation are maintained for the sole purpose of ensuring organ viability, until definitive organ-preservation measures can be initiated in the hospital.

Figure 12.1. **The key steps in the process of uncontrolled donation after circulatory death**

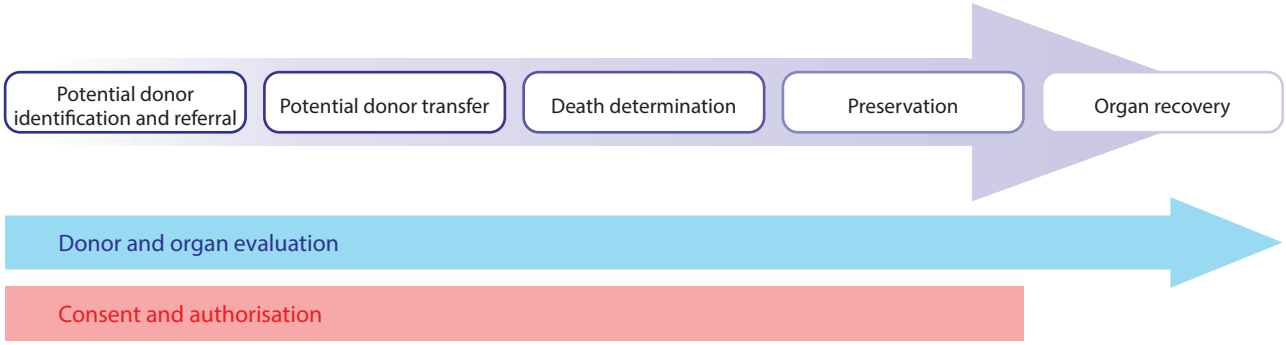
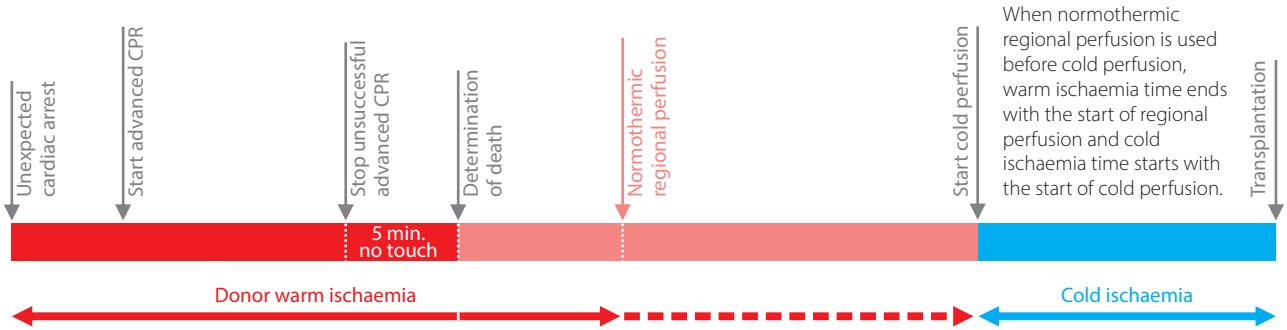


Figure 12.2. **Process of uncontrolled donation after circulatory death, specifying limits of warm and cold ischaemia time**



Note: The most commonly adopted no-touch period is 5 mins, but it may be different in some jurisdictions.
CPR: cardio-pulmonary resuscitation.

Chest compression, performed either manually or with mechanical devices, is allowed in existing programmes. Although there is no evidence that organ viability is improved with the use of mechanical devices, the quality of the chest compression has been shown to be better than with manual chest compression [38].

If needed, the out-of-hospital emergency service may require the support of the police or other agencies during donor transfer for swift transportation.

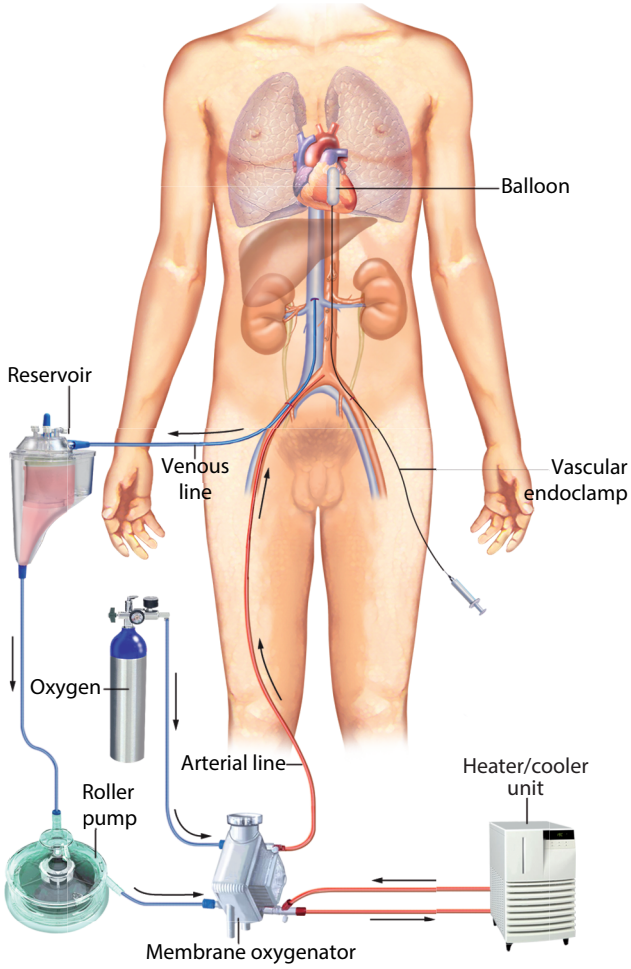
Complete information about the quality of these manoeuvres for preservation purposes is desirable. If possible, values of end-tidal CO_2, pH at the beginning and during transfer, lactic acid, etc., must be recorded. This will be helpful for the transplant team when they later assess the quality of the preservation measures and of the organs to be used for transplantation purposes.

12.2.3. Determination of death

Existing programmes of uDCD base the determination of death on two prerequisites: an exhausted advanced CPR as described in international standards (including at least 30 min of advanced CPR); and cessation of spontaneous circulation (absence of electrical activity on ECG, absence of aortic flow on the echocardiogram or absence of pulse) for a minimum observation period that varies from country to country, although 5 min is most common time interval recommended in clinical practice. These criteria for the determination of death differ from the standards developed in countries focused on cDCD, where the permanent cessation of circulation ('will not return') is used as a surrogate for the irreversible cessation of circulation ('cannot return') for the diagnosis of death [44-47]. The difference is that, in uDCD, CPR has been applied and is unsuccessful, whereas in cDCD there is a cessation of supportive therapy. These different approaches to the determination of death have been discussed internationally [48-51].

Death by circulatory criteria should be confirmed by professional(s) who are not part of the retrieval or transplantation team. In practice, this is usually done by the team taking over the CPR manoeuvres for patients transferred from the out-of-hospital setting. Hence, even if CPR has been considered unsuccessful in the street, death is determined in the hospital.

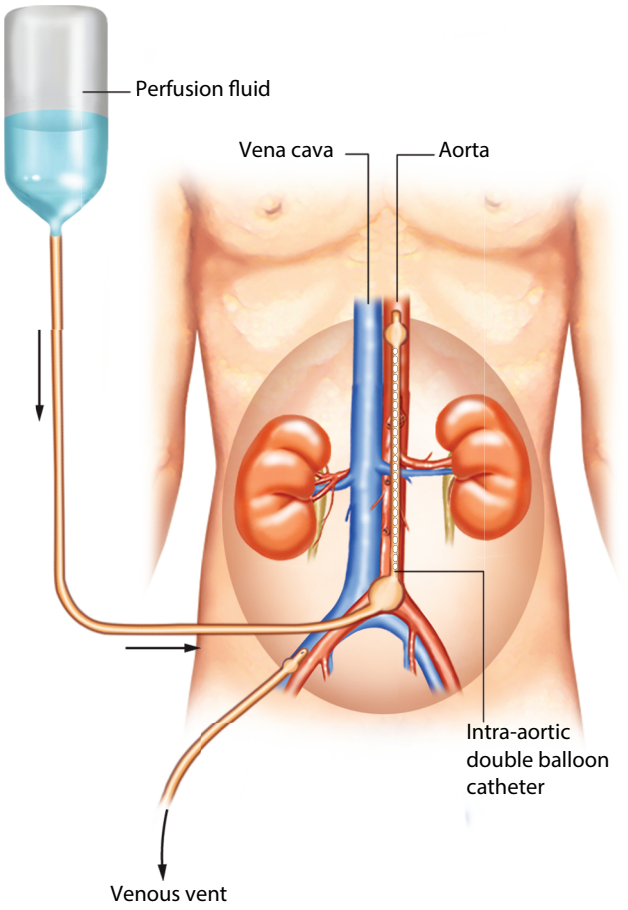
Figure 12.3. **Regional perfusion circuit and heat exchanger with a vascular catheter incorporating an aortic endoclamp placed in correct position to establish hypothermic or normothermic regional perfusion**



12.2.4. *In situ* preservation and organ recovery

Once death has been determined and certified, existing programmes vary in their approaches to maintaining organ viability. In some countries, cardiac compression and mechanical ventilation are recommenced until the donor is transferred to the operating room where definitive *in situ* preservation manoeuvres are established. In other countries, resumption of cardiac compression and mechanical ventilation is avoided [14, 20, 41]. If cardiac compression and mechanical ventilation are restarted after death is confirmed, it is also recommended that a bolus of sodium heparin 500 IU/kg be administered before *in situ* preservation strategies are initiated. Other anticoagulant strategies are currently being explored but there are no data to support their benefit.

Figure 12.4. ***In situ* cooling preservation of kidneys with the double-balloon triple-lumen catheter technique**



12.2.4.1. *Abdominal preservation procedure*

There are two different strategies for the *in situ* preservation of abdominal organs in uDCD: hypothermic regional perfusion (HRP) or NRP, based on the use of ECMO devices; and the *in situ* cooling of organs. The two procedures are described below.

12.2.4.1.1. Hypothermic or normothermic regional perfusion

This procedure, establishing a femoro–femoral bypass extracorporeal circulation with membrane oxygenation, entails the following processes (see Figure 12.3):

a. Cannulating the femoral vein and artery of one leg for the connection to an extracorporeal circulation system, which includes a membrane oxygenator and temperature exchanger.

b. Introducing an endo-aortic balloon into the descending thoracic aorta, via the contralateral femoral artery, to restrict preservation to the abdominal cavity.

c. Simultaneously introducing the prime solution and premedication in the extracorporeal circulation pump. This should be finished before cannulation is completed.

d. Inflating the endo-aortic balloon before establishing HRP or NRP, once the correct position of this catheter has been checked radiologically.

The maximum duration of HRP or NRP in uDCD procedures has been established empirically at 240 min in most of the existing programmes. This is now supported by experimental evidence [52]. If liver donation is planned, NRP should be established, rather than HRP. If lung donation is planned, HRP is preferred, to avoid warming the thoracic cavity. Dual temperature – HRP for thoracic organs and NRP for abdominal organs – is feasible, allowing more organs to be recovered, but there is limited information on the results of lung and liver transplants using this strategy [37, 53]. The available evidence suggests that kidneys can be recovered using both HRP or NRP.

In situ preservation manoeuvres based on HRP or NRP should be discontinued in the following situations:

- When the necessary consent and authorisation requirements for organ recovery have not been obtained.
- If, after 240 min of HRP or NRP, the necessary requisites for organ recovery (i.e. consent and authorisation) have not been fulfilled.

12.2.4.1.2. *In situ* cooling preservation with the double-balloon triple-lumen catheter

This method uses a double-balloon catheter that is placed in the aorta, with one of the balloons inflated above the diaphragm (above the level of the renal arteries) and the other balloon inflated at the aortic bifurcation (see Figure 12.4). The renal vascular tree is exsanguinated and then perfused with a high-flow preservation solution at 4 °C. In this way, kidneys can be obtained for transplantation within 2 h. This method does not allow recovery of the liver for transplantation with acceptable results, but it is compatible with lung donation. Once preserved through any of the methods described above, kidneys and/or liver are recovered using the usual surgical techniques. From this moment on, there is no difference from organ recovery in the DBD setting (see Chapter 11). The cold ischaemia time should be minimised as much as possible.

In situ cooling of uDCD donor kidneys has yielded acceptable results, but has been associated with an increased risk of PNF and DGF compared with HRP/NRP, and it is not deemed an acceptable strategy for uDCD livers, where NRP is considered critical [20-22]. With the use of NRP and highly se-

lected donors and recipients, promising results have been obtained in uDCD livers, although inferior to those obtained with DBD livers [26-28, 30, 54].

A study from Nantes and Angers in France compared NRP (n = 19) with SCS (n = 31) in kidneys from Maastricht category II uncontrolled DCD donors. All kidneys underwent HMP for at least 2 hours following NRP. PNF as well as patient and graft survival rates did not differ between the groups. However, the use of NRP was associated with a significantly lower risk of DGF compared to SCS (53 % *versus* 81 %, p = 0.036), which persisted in multivariate models (adjusted OR = 0.17, 95 % CI 0.03-0.87, p = 0.034). Furthermore, the use of NRP was the only significant factor associated with a likelihood of an estimated glomerular filtration rate (eGFR) > 40 mL/min/1.73 m^2 at year 1 post-transplantation (adjusted OR = 3.68, 95 % CI 1.06-12.8, p = 0.04) [17, 55].

In Russia, sub-hypothermic (27-32 °C) regional perfusion that includes leukodepletion and thrombolysis has been started at up to 60 minutes of no-touch period and achieves kidney transplant outcomes similar to those from DBD donors [56].

12.2.4.2. *Lung preservation procedure*

Lung recovery and transplantation has been successfully developed in experienced uDCD programmes. There is a specific method to preserve the lungs of uDCD donors, based on topical cooling, developed in Spain [35-36]. Currently, dual preservation (cooling up above the diaphragm and normothermia below the diaphragm) is possible, although experience is still preliminary [37, 40]. Further work is needed to develop the optimal conditions to enable the concomitant recovery of abdominal and thoracic organs. Lungs are preserved as follows:

a. A 300 mL volume of venous blood is collected into a heparinised bag via the venous cannula, prior to starting the pump.
b. A bronchoscopy is performed in the operating room and ventilation is stopped when the potential donor is placed on the extracorporeal circuit and the endo-aortic balloon is inflated.
c. Two anterior pleural drainage tubes are introduced (2nd intercostal space, mid-clavicular line) and instilled with preservation solution at 4 °C, until the pleural cavities are completely filled and the lungs collapse (5-6 L per hemithorax). Two additional tubes may be placed at the 5th intercostal space, mid-axillary line, to allow the perfusion solution to recirculate through the heat exchanger to maintain a lower preservation temperature of the lungs. A maximum time of 3 h is allowed before initiating lung recovery.
d. Thoracic temperature must be monitored through an oesophageal probe.

Usually, this method allows temperature to remain stable between 10 °C and 15 °C, which is excellent to preserve lungs until recovery.

Once lungs are preserved and consent/authorisation has been obtained, the recovery procedure follows as described below:

a. The pleural cavities are drained and ventilation is restarted with FiO_2 1.0 and positive end-expiratory pressure (PEEP) + 5 cmH_2O. As the lungs are cooled, initial ventilation is applied with a low respiratory rate and tidal volume of 3 mL/kg in order to avoid vessel damage; the tidal volume is later increased slightly. Once normal ventilation has been established, the thoracic surgeon performs a bronchoscopic evaluation and assesses the compliance on the ventilator. Macroscopic evaluation is then carried out, noting the appearance and weight of the lungs before performing the so-called collapse test by disconnecting the endotracheal tube from the ventilator. The pulmonary artery is cannulated so that the lungs can be flushed until the effluent from an incision in the left atrium is clear.
b. The lungs are then perfused with the venous blood withdrawn previously from the donor via the pulmonary artery. At this point, blood samples are taken from each pulmonary vein (from the left auricle) for blood-gas determination (pvO_2) while ventilating with FiO_2 1.0 and PEEP +5 cmH_2O. Each lung is assessed separately, testing the blood samples from each vein. The intrathoracic temperature is determined using a disposable oesophageal probe for temperature correction of the pvO_2/FiO_2 ratio.
c. The lungs are considered suitable for transplant if adequate oxygenation can be observed. This is defined as a difference (gradient) of pO_2 greater than 350 mmHg between pulmonary artery (paO_2) and pulmonary vein (pvO_2).
d. The recovery of lungs is performed as in the DBD setting, with a similar surgical technique, through a medial sternotomy.

In Canada, a technique of retrieving lungs up to 3 hours after unsuccessful resuscitation without the need for topical cooling has been developed. It involves prone positioning and the application of continuous positive airway pressure (CPAP) to re-inflate

the lungs and keep them inflated until retrieval followed by *ex situ* lung perfusion for further evaluation [57]. Recently a new technique for providing the optimal conditions to enable the concomitant recovery of abdominal organs and the lungs, without the requirement for cooling the lungs, has been described for cDCD in Italy [58].

12.2.5. Consent and authorisation process

The process of obtaining consent to organ recovery (and preservation where appropriate) in uDCD must be adapted to the legislation and practice applicable in a given jurisdiction, including the type of consent system in place (see Chapter 4) [14].

In countries with opt-out legislation (presumed/deemed consent), establishing consent is focused on establishing the lack of any expressed objections to organ donation during the potential donor's lifetime. For this purpose, relatives are interviewed and existing registers are consulted. However, donation is facilitated by the existing legal framework. In uDCD, consent may be obtained at different time points along the process: as soon as the irreversibility of the cardiac arrest is established by the emergency service, or when *in situ* preservation measures have started. Organ recovery must never proceed before consent is obtained.

In countries with an opt-in system, the practice is to assess whether the person has expressed a choice about organ donation. The national registry must be consulted to assess the person's wishes. In uDCD, the registry may be consulted as soon as the emergency service announces that a potential donor is being transferred to the hospital. In cases of any registered objection to donation, the process is stopped. If no objection to donation is identified, *in situ* preservation measures after death can commence, even if the family has not been consulted yet. If positive consent is identified, organ recovery can be continued after the family has been informed. If the patient's wishes are unknown, the family will be asked to give permission. Organ recovery is not continued if the family opposes it or if the family interview cannot be held within the first 2 h following the initiation of preservation measures.

12.2.5.1. *Family interview*

Communication with the family is particularly challenging in uDCD. While death confirmed using circulatory criteria is easier for a family to understand than brain death, the unexpected nature of the CA makes the circumstances distressing for the relatives and professionals.

Families are faced with the completely unexpected death of their loved one and soon afterwards are asked to consider the option of donation. Transparency in communication is paramount during the entire process, but the information should be provided progressively and in a manner adapted to the emotional and other needs of the family [59-60].

The family interview is dealt with as an intervention in a moment of crisis and seeks to resolve the problems that arise in such stressful circumstances. People in crisis often feel unable to deal with the situation. Well-administered support can help manage these feelings and help the person make a decision. It must be accepted that, at this moment, distress and lack of information are the greatest difficulties to overcome. Through 'active listening' and 'an offer of help', the interviewer seeks to generate a relationship with space for an exchange of information and for thinking about the idea of organ donation, helping the family to make an informed decision.

The family must be accompanied and supported from the moment they reach the hospital. If the family were present at the moment of death, as in the case of a sudden death at home, the out-of-hospital emergency service must evaluate the possibility of informing the family there and then about the possibility of organ donation. This is not always possible, because often there is no relative near the potential donor or the situation does not allow presentation of complex information. The donor co-ordinator must offer the family a quiet and isolated environment to give them privacy and comfort. The whole information process must be transparent, and any questions the family has about the death of their relative must be answered.

Once consent has been given, a follow-up period is established in which the needs of the donor's family can be periodically attended to.

For further information on the family interview, see Chapter 4.

12.2.5.2. *Judicial authorisation*

uDCD donors are frequently within the scope of a judicial or forensic medical investigation if death has occurred in the context of a traffic or occupational accident or if the cause of the CA is unclear. Insurance policies need to be attended to and a crime incident has to be ruled out. Given the time constraints of the uDCD process, a procedure should be established for judicial/coroner authorisation in order to proceed with *in situ* preservation manoeuvres and organ recovery in this setting.

12.2.6. Continuous evaluation

Evaluation and validation of uDCD donors is done according to general inclusion criteria for organ donation, along with the specific selection criteria for each organ (see Chapter 6 and Chapter 7). Additionally, criteria specific to uDCD must be taken into account, as summarised in Table 12.3. As in DBD, donor and organ evaluation are based on a review of the past and present medical history and the presence of high-risk behaviours in the potential uDCD donor, as well as a physical examination and complementary tests. Available medical records and charts must be carefully reviewed. A dedicated and guided interview with the relatives should always take place for assessment of the donor's suitability.

Donor evaluation can be facilitated by the out-of-hospital emergency service in several ways. Usually, blood samples are taken once death has been determined. However, potential uDCD donors are frequently haemodiluted when CA occurs outside the hospital environment and is followed by transfer to hospital. To ensure that non-haemodiluted samples are available for donor evaluation, e.g. serology, some programmes have incorporated into the out-of-hospital emergency service protocol the recovery of blood samples once the uDCD procedure is activated. These early samples are also of value when potential donors have exsanguinating lesions, preserving the option of lung donation.

12.2.7. Organ-specific evaluation criteria (see also Chapter 7).

12.2.7.1. *Kidney evaluation criteria*

For kidneys, the history of the donor is the cornerstone of the consideration of donation. Of course a history of renal disease is a formal contraindication for donation (for more information on organ-specific contra-indications, see Chapter 7). Biochemical determination at arrival, mainly values of serum creatinine and urea, can help in the decision regarding kidney donation. *Ex situ* hypothermic non-oxygenated pulsatile preservation of kidneys is today used in many uDCD programmes. When using pulsatile machine preservation, a resistance index below 0.4 mmHg/mL/min/100 g and a flow above 70 mL/min are indicative for using the kidneys. This resistance index must be considered together with other kidney validation criteria, including biochemical, anatomical and histological assessments.

12.2.7.2. *Liver evaluation criteria*

The liver is very sensitive to ischaemia and is the most difficult organ to recover in uDCD. NRP may facilitate ischaemic preconditioning of organs, and also allows assessment of the evolution of liver enzymes – alanine transaminase (ALT) and aspartate transaminase (AST) – as a marker of organ injury. The initial Spanish experience suggested that during abdominal NRP a pump flow greater than 1.7 L/min combined with ALT/AST levels below three times the upper normal values at the beginning of NRP, and less than four times the upper normal value at the end of NRP, were indicators that the liver could be recovered and successfully transplanted [28].

There are some *ex situ* devices for liver preservation, but at present there is not enough evidence to establish markers or monitoring values to help decisions regarding liver viability in uDCD. Validation should be based on general and specific selection parameters, as well as on macroscopic evaluation of the organ and histology.

12.2.7.3. *Lung evaluation criteria*

For lung validation, the orotracheal tube must be clear of blood and purulent secretions on admission to hospital and there must be no evidence of bronchial aspiration. Chest X-ray must be clear, with no mass or infiltrates. Validation of lungs from uDCD donors based on gas exchange has been summarised in section 12.2.4.2. There are devices available to preserve lungs *ex situ*, assessing their capability of oxygenation and preserving organs through a longer cold ischaemia period. An appropriate gas exchange should be confirmed.

There is no experience with the transplantation of other organs in the uDCD setting. Special consideration must be given to the potential of uDCD programmes to contribute to tissue donation.

12.3. Controlled donation after circulatory determination of death

In cDCD, CA occurs following a planned WLST after it has been determined and documented that continuing invasive organ support is no longer in the best interests of a critically ill patient and in accordance with the patient's personal preferences and values [61]. Unlike uDCD, in cDCD the CA is anticipated and expected, which allows the donation procedure to be planned. cDCD can therefore take place in any hospital that has an ICU and facilities for surgery. Unlike uDCD, in cDCD the patient is still alive while the donation process is being organised. Clear and robust policies supported by professional bodies and by legislation are required to ensure that

best practices in end-of-life and palliative care can continue to be provided at a time when interventions to minimise warm ischaemia are also being considered and implemented. Healthcare staff can be particularly uncomfortable in this scenario where end-of-life care and donor care in effect overlap. The challenge in the practice of cDCD is not only to identify patients suitable as potential donors, but also to support and maintain the trust of grieving families and the wider society, and to decide how best to minimise the consequences of warm ischaemia in a fashion that is professionally, ethically and legally acceptable.

In countries practising cDCD, these donors have become an increasingly important source of organs for transplantation [7]. (see Table 12.2 and Chapter 1, Figure 1.1). The potential for cDCD varies between countries, with the biggest determinant being the frequency of decisions in favour of WLST in critically ill patients. The Ethicus study, conducted at the beginning of this century, highlighted the variation in end-of-life care practices across Europe, with WLST being decided nearly three times more frequently in northern European countries, such as the Netherlands and the United Kingdom, as in southern European countries, such as Italy and Spain [62]. It also found that the incidence of brain death was nearly four times more frequent in these southern countries than in the northern European countries. The Ethicus study has been recently repeated. Although variations in end-of-life care practices persist across European regions, it seems that withholding and withdrawing life-sustaining treatments are becoming more frequent, including in southern countries [63].

It is not just the frequency of WLST that makes a difference to donation practices, but also the timing of that decision after ICU admission. It is accepted that DBD is the preferred deceased organ donation pathway because more organs are utilised, including more cardiothoracic organs than from cDCD donors [7]. Early WLST means that some patients with catastrophic brain injuries will not deteriorate to brain death, precluding the potential for DBD. DBD donors are not being lost by the introduction of cDCD programmes [64]. However, one study estimated that up to 30 % of actual cDCD donors had the potential to progress to brain death and DBD if the WLST had been delayed by a further 36 h, an intervention that needs professional and family support [65]. This also highlights how changes to end-of-life care practices, within an appropriate legal and ethical framework, have the potential to improve organ donation. In countries where this is relevant, the issue of early WLST can be addressed by adoption of devastating brain injury pathways. These are primarily to improve prognostication by the delay in WLST. This also allows time for progression to brain death in 31 % of patients admitted to the ICU with such a pathway [66]. This brings about the secondary benefits of increasing the total number of organ donors and the proportion of DBD donors [66], and it potentially increases the total deceased donor pool [12].

cDCD has become an increasingly important source of organs for transplantation in countries like Austria, Australia, France, Canada, Belgium, the Netherlands, Spain, the United Kingdom and the United States. For example, between 2011 and 2018 the annual number of actual DCD donors increased from 405 to 636 in the United Kingdom [67], and France has had 409 utilised cDCD donors in the last 5 years. In 2019 in the Netherlands, 59 % of all deceased donors were cDCD donors while in Spain cDCD donors contributed to 32 % of the overall deceased donation activity in 2019; and in Austria the number of utilised DCD donors tripled from 2017 to 2019.

A key issue is whether grafts recovered from cDCD donors are equivalent in quality to grafts recovered from DBD donors, due to combination of warm and cold ischaemia in the donor. DGF is more common in transplanted kidneys recovered from cDCD donors, but the long-term outcome in terms of survival and kidney function is similar to that of kidneys recovered from DBD donors [68-69]. Moreover, a recent United Kingdom registry study made evident that results of kidneys from cDCD donors with expanded criteria were broadly similar to those obtained with expanded-criteria kidneys from DBD donors [70]. The frequency of DGF in kidney transplantation from cDCD donors can be decreased by reducing the duration of cold ischaemia [71] and potentially through the use of NRP for *in situ* preservation or *ex situ* machine perfusion [20]. Pan-European data on 11 102 DCD kidney transplants show that transplant outcomes are better when the kidney was recovered from a cDCD than an uDCD donor. Recipients of a cDCD kidney have an incidence of PNF of 2.8 %, a DGF rate of 30.7 % and a one-year graft survival of 90.1 % compared to 7.4 %, 52.6 % and 88.1 % respectively in recipients of an uDCD kidney [7].

The outcomes of liver transplantation from cDCD donors are also considered acceptable, with a 3-year patient survival rate of 63 %, compared to 72 % for recipients of livers from DBD donors. However, between 10 % and 15 % of the grafts are lost within the first year post-transplant (patient death or relisting for transplantation, United Kingdom NHSBT

data). In fact, large registry data have identified DCD as an independent risk factor for graft loss in liver transplantation [72-74]. The incidence of primary graft failure is increased to 4 % in recipients of a liver from a cDCD donor compared to 0.8 % in recipients of a liver from a DBD donor. However, the primary concern with cDCD liver utilisation is a significantly higher incidence of biliary complications, particularly ischaemic-type biliary lesions (ITBL) which are associated with longer WIT [75-79]. Many of these patients require re-transplantation. Long-term follow-up of cDCD liver transplantations in Belgium and the Netherlands has shown similar results. In an early analysis of European data from 126 cDCD transplants, graft survival was poorer than DBD livers although graft survival curves appeared to converge at 10 years; patient survival was also similar in spite of cDCD liver recipients having a higher risk of re-transplantation [80]. This is likely due to strict donor and recipient selection criteria for DCD livers and the weighting given to other risk factors to reduce these complications and optimise outcome. The use of *in situ* NRP has recently been shown to reduce graft loss, biliary complications and ITBL after cDCD liver transplantation in two large, multicentre studies undertaken in Spain and the United Kingdom [81-83]. *Ex situ* hypothermic [84] or normothermic machine perfusion [85, 86] of the liver have also shown very promising results in mitigating the ischaemia-reperfusion injury, and short-term outcomes seem to reach similar results as from DBD livers.

Although DCD is an independent risk factor for inferior outcomes after pancreas transplantation [87], results can be excellent if other risk factors are kept low. Results from a short-term comparative study on pancreas transplantation from cDCD and DBD donors in the United Kingdom reported similar one-year pancreas and recipient survival rates for transplants from cDCD and DBD donors, with pancreas graft survival being significantly better in the cDCD cohort if performed as a simultaneous pancreas–kidney transplant [87]. Similar promising results have been published with data derived from the OPTN/UNOS Registry [88]. A recent meta-analysis has also shown comparable graft and patient survival for cDCD and DBD pancreas grafts [89].

Theoretically there may be advantages to transplanting lungs recovered from cDCD donors, since they have not been exposed to the deleterious cardiopulmonary effects caused by the autonomic storm that accompanies brain stem coning before brain death (see Chapter 5), although accumulating animal and human data do suggest that this still occurs during the withdrawal period [90]. The lungs also appear to be more tolerant of warm ischaemia than other organs as long as they are kept inflated with an air–oxygen mixture [91]. The consequences of warm and cold ischaemia may be further reduced by the use of *ex situ* lung-perfusion techniques. Indeed, initial results from the United States suggest that survival is better for recipients of cDCD lungs than for recipients of DBD lungs, with 2-year survival rates of 87 % and 69 %, respectively [92]. However, it is recognised that variations in donor and recipient selection criteria and surgical techniques may make comparison of outcomes difficult. A more recent large registry study from 22 large centres in North America, Europe and Australia reported outcomes of 11 516 lung transplants, 1 090 of which were DCD lungs (94 % cDCD). The study used multivariate analysis to control for many of these factors and showed no difference in 5-year survival between recipients of DBD and cDCD lungs [93]. Simultaneous retrieval of the lung and liver in cDCD using NRP for abdominal grafts and cooling and rapid recovery technique for the lungs is a complex procedure, but has been used safely and successfully [94].

Figure 12.5. **The key steps in the process of controlled donation after circulatory death**

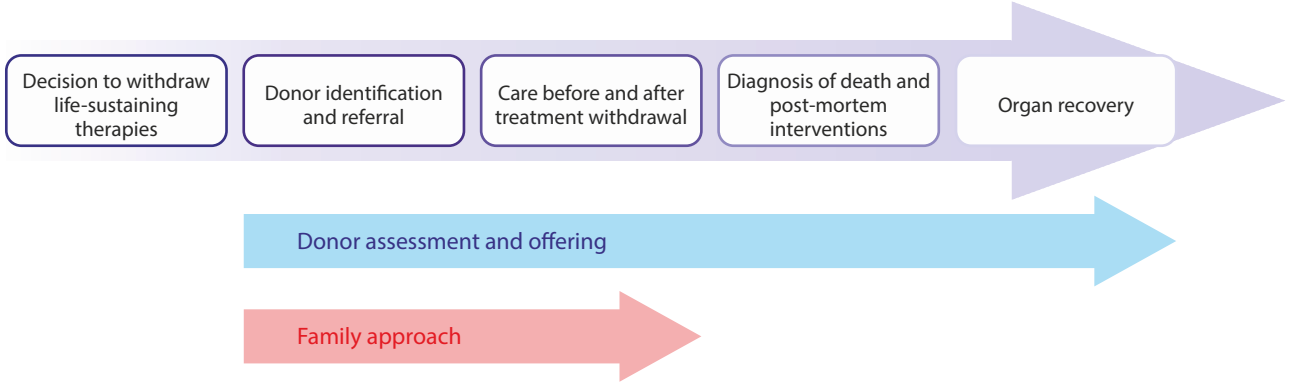
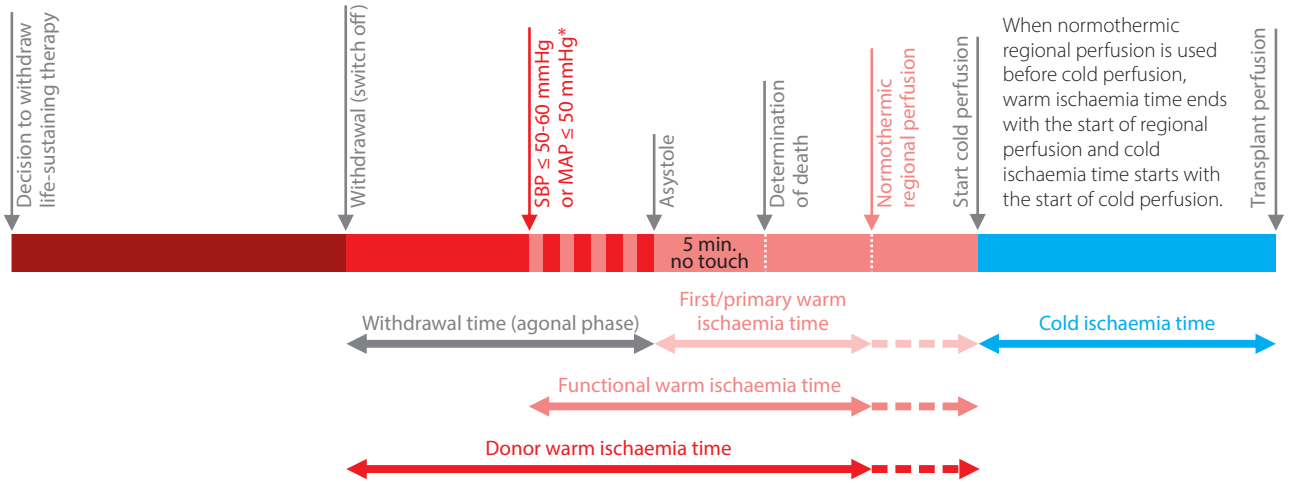


Figure 12.6. **Process of controlled donation after circulatory death, specifying limits of warm and cold ischaemia time**



* There is no general consensus for a cut-off value for the start of functional warm ischaemia time. Currently this is mostly in the range of the values shown for systolic blood pressure (SBP) or mean arterial blood pressure (MAP) but the ideal measure is yet to be defined. Note that 5 min is the most commonly adopted no-touch period, but this may vary from 5 to 30 min across Europe [7].

More recently, hearts recovered from cDCD donors have been successfully transplanted in Australia [95], the United Kingdom [96] and Belgium [97]. The results of cDCD donor heart transplantation using either direct (hypothermic) procurement and perfusion (DPP), thoraco-abdominal NRP (TA-NRP) and/or *ex situ* normothermic machine perfusion appear to be at least equivalent to those with DBD hearts in short and mid-term follow-up, with a current world experience of 90 cDCD donor hearts transplanted in the United Kingdom by March 2019 (data from NHSBT), 30 in Australia [98], 2 in Belgium [97] and 5 paediatric hearts in Colorado (United States). The long-term results of this encouraging initiative are eagerly anticipated.

The process of cDCD is summarised in its key steps in Figure 12.5 [99]; the steps from decision on WLST to transplant reperfusion are shown in Figure 12.6.

12.3.1. Withdrawal of life-sustaining therapies

The decision to withdraw treatment should always be made in accordance with national guidance on end-of-life care. All such documents recognise the fundamental principle that a decision on WLST must always be made in the best interests of the patient and independent of any subsequent consideration of organ donation. No member of a donor co-ordination team may be involved in this decision-making. For example, in the United Kingdom it is considered good practice for two senior doctors to independently verify and document in the medical notes that further active treatment is no longer in the patient's best interests whenever a decision on WLST is being made, but particularly when cDCD is a possibility [100]. National end-of-life care guidance that recognises organ donation as a routine part of end-of-life care [101] is helpful in reducing the perception of any conflict of interest, even though none may exist. It also makes it clear to medical practitioners that they are obliged to follow national procedures for identifying potential organ donors and referring them to the donor co-ordinator.

Individual hospitals should develop guidelines for treatment withdrawal based on the national guidance. Although the need to develop and comply with such protocols applies to all end-of-life care decisions, it is particularly important that units practising cDCD make the process consistent and transparent. These protocols should not only address the principles of the decision-making process but also give practical guidance on how to manage treatment withdrawal, particularly with regard to airway management and the use of sedative and analgesic medications. While there may be variability in current critical care practice on these issues, the interests of a patient who wishes to be a donor may be better served by end-of-life care practices, such as extubation, that make organ donation more likely and, importantly, represents no actual harm to the patient or their relatives [102]. Transplant teams must not advise on how treatment should be withdrawn.

If the family agrees, WLST must be delayed until a retrieval team is ready and prepared in the operating theatre. Those responsible for organ alloca-

tion and recovery should do all they can to minimise delays, recognising the needs of the donor and their family at this time. The location of WLST also needs to be considered. When this occurs in the theatre complex, which is essential for recovery of cDCD hearts, WIT is reduced by avoiding transferring the donor from ICU to theatre after death [102]. However, it is important that this practice does not compromise the delivery of end-of-life care, and units that choose to undertake WLST in theatres should ensure that appropriately trained healthcare professionals continue to provide this care rather than expecting theatre staff, who may be untrained and inexperienced in end-of-life management, to do so. Arrangements should also be in place to ensure access for close family, friends and those meeting the religious or spiritual needs of the patient [103].

cDCD can only take place if cardio-respiratory arrest follows soon after WLST. This time limit is most commonly around 2–4 h. Although up to 84-90 % of cDCD donors will have died within 2 h of WLST [104-105], successful kidney recovery has occurred more than 4 h after WLST in circumstances where the functional warm ischaemic time (FWIT) has been acceptable [106]. Examples of registration forms can be found in appendices 23 and 24. Retrieval teams need to work to nationally agreed standards to ensure that organs are not lost unnecessarily and also to maintain the confidence of referring units. The reasons for standing a donation down should always be documented for audit and also for the information of the referring team.

A clear plan must be in place for the subsequent continuation of end-of-life care of the patient when donation cannot take place, particularly when WLST has taken place outside the ICU.

12.3.2. Patients receiving extracorporeal life support

ECLS is being increasingly used, particularly in the management of refractory CA, and more patients in ICU or the emergency department will be receiving ECLS as part of their continued management. Patients who do not survive may progress either to brain death or to a decision on WLST, which in this case involves stopping mechanical ventilation and ECLS. Since WLST in these circumstances is also planned and death is anticipated, this can be classified as a Maastricht Category 3 DCD. The WLST follows national and local guidelines as described above. The only additional step is to stop ECLS, and death is confirmed in the usual manner. If the patient is a potential cDCD donor, the ECLS arterial and venous cannulae should be left in place so that, if required, HRP or NRP can be commenced quickly once death is confirmed and steps have been taken to exclude cerebral perfusion.

12.3.3. Identification of potential donors

The potential for cDCD should be considered in any critically ill patient where a decision of WLST has been made (see Chapter 2). Most cDCD donors have suffered severe acute brain injury of aetiologies similar to DBD donors, although there is a higher proportion of hypoxic brain injuries among cDCD donors. When identifying such patients as potential cDCD donors, it is important to consider whether death by neurological criteria can be confirmed while cardio-respiratory stability is maintained and the WLST is delayed. If brain death is likely to occur within a short period of time, consideration should be given to maintaining life-support measures beyond futility to enable the determination of death by neurological criteria [62, 107]. Although the majority of actual cDCD donors die from acute brain injury, data from Spain and the United Kingdom suggest that 4 % to 15 % of cDCD donors die from other conditions such as end-stage respiratory failure or neuromuscular diseases [22].

Clear practical guidance for the identification and referral of potential cDCD donors should be developed, specifically addressing who should be referred as a potential donor, when the referral should take place and how the patient should be cared for while initial assessments of donation potential are made. The guidance should ensure that identification and referral can be made without causing clinicians caring for dying patients to feel that there is a potential conflict of interest. Ideally the donor co-ordinator should be notified whenever a decision on WLST is being considered, because this may allow background enquiries to be made and potentially reduce the delay in WLST and any distress this may cause relatives. It also allows the approach to the family to be planned. Examples of how this can be achieved in practice can be found in NHS Blood and Transplant's document on 'Timely identification and referral of potential organ donors: a strategy for implementation of best practice' [108]. See also Chapter 2.

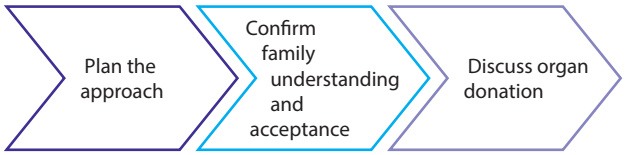
The development of an accurate and reliable scoring system, capable of predicting whether death after WLST will occur within a time period compatible with cDCD, would reduce the number of donations that are stood down, avoid family distress, increase the efficient use of retrieval teams and reduce the burden on critical care services. Individual

donor hospitals and transplant centres may choose to use systems like the University of Wisconsin and the UNOS scoring systems [109-110] when deciding to refer or accept individual potential cDCD donors. However, it is currently impossible to reliably identify potential cDCD donors who will die within 2 h after WLST [111]. Consequently, centres may choose to initiate a donation process in every potential donor.

12.3.4. Consent and authorisation

Potential cDCD donors usually lack the capacity for decision-making while being cared for in an ICU or emergency department. On rare occasions, for instance when withdrawing ventilatory support from a competent patient with end-stage neuromuscular disease or respiratory failure, or in cases of cDCD following euthanasia, it will be possible to obtain first-person consent by discussing donation directly with the patient. On most occasions the patient's relatives will need to be approached for organ donation. National end-of-life care guidance should be explicit in that, if a patient is close to death and their views cannot be determined, medical staff should explore with the relatives whether the patient had expressed any views in life about organ or tissue donation and/or if donation was consistent with their moral values. The approach for cDCD should take place in three stages (see Figure 12.7) [112].

Figure 12.7. **The three discrete stages in approaching the family of a potential controlled donation after circulatory death donor**



Source: NHS Blood and Transplant 2013. Approaching the families of potential organ donors. Best practice guidance [112].

The approach should be planned between the medical and nursing staff caring for the patients and the donor co-ordinator to clarify the clinical situation, identify key family members, define key family issues, seek evidence of prior consent (e.g. checking donor registries), agree the timing and setting of the approach and agree who will be involved. The approach should not be made until the clinical team is satisfied that the family understands and accepts the reasons for treatment withdrawal and the inevitability of death thereafter. To ensure this, the conversation on withdrawing treatment should be decoupled from the approach for organ donation. This also helps reduce any perception that a decision on WLST is linked to a need for donor organs.

However, it may not always be possible to completely separate discussions about treatment withdrawal and discussion of donation, particularly if the family raises the issue of donation themselves. The final stage is discussing donation, which should ideally be led by someone experienced in organ donation and who is trained in communication with grieving families, usually the donor co-ordinator [113]. He or she will discuss options, provide knowledge and expertise, recognise modifiable factors, challenge misconceptions, provide support for the family and spend time with the family. The donor co-ordinator will also collect all the information required to assess whether the patient is suitable for donation and may discuss whether certain *ante mortem* and/or *post mortem* interventions are acceptable to the family [114]. See also Chapter 4.

12.3.5. Care before and after treatment withdrawal

cDCD is only possible if elements of the care that a patient receives both before and after WLST are adjusted. Changes to end-of-life care before the patient dies must continue to be made in the patient's best interests and in accordance with national, legal and professional guidelines. Any such change to routine end-of-life care to facilitate cDCD is in effect an *ante mortem* intervention and there is variability among countries as to what is considered acceptable [115]. Most such changes are applied to reduce both warm and cold ischaemic damage to the organs.

Ante mortem interventions can be justified, both ethically and legally, on the grounds of best interests if they facilitate the wishes of a patient to donate, and if any potential for harm or distress to that patient or their relatives can be reasonably controlled [116-117]. In general, the stronger the evidence that an individual intervention improves donation or transplant outcomes and the smaller the risk of that intervention being harmful, then the more acceptable that intervention is. Conversely, interventions with weak evidence of improving outcomes, and with a bigger chance of causing harm, are less likely to be justifiable [117]. The views of the patient's relatives are also relevant in assessing this balance. Each country needs clear legal and/or professional guidance as to which *ante mortem* interventions are considered acceptable and which interventions should be accepted with the specific consent of family after appropriate information has been given. The guidance should be specific about the role of the donor co-ordinator in

cDCD. Donor co-ordinators have an important role in donor management and optimisation in DBD, but there is a clear risk of being conflicted if they are involved in the care of a potential cDCD donor. As a result, many policies generally do not allow a donor co-ordinator to be involved in the physical treatment of potential cDCD donors or in the management of WLST.

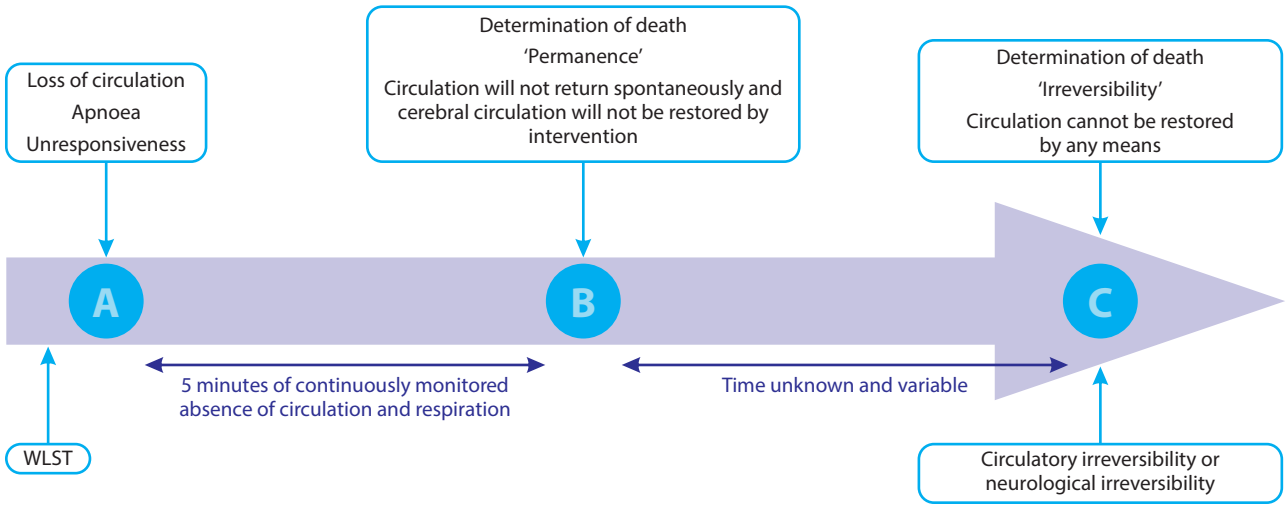
After the death of the patient, further interventions are quickly undertaken before or during the recovery operation, to reduce the ischaemic time or to optimise organs before transplantation. cDCD protocols should acknowledge the potential risks associated with *post mortem* interventions that may restore cerebral perfusion with oxygenated blood. Most cDCD protocols allow the recovery procedure and organ perfusion with cooled crystalloid or colloid solutions as soon as death has been confirmed (after the recommended time of evidence of continuous absence of circulatory and respiratory functions). NRP procedures can reduce the warm ischaemic damage to vulnerable transplantable organs by recirculating the abdominal and thoracic organs with oxygenated blood prior to explantation. Protocols applying such interventions should describe how reperfusion will be reliably restricted to the relevant organs, and how the cerebral circulation is excluded by the use of vessel clamps, intravascular balloons or diversion of collateral blood flow away from the brain [117-121]. If the lungs are to be recovered from a cDCD donor, the trachea needs to be re-intubated and the lungs inflated after death.

12.3.6. Determination of death

It remains absolutely fundamental to the practice of all types of deceased organ donation that the dead donor rule – the requirement that organ recovery must not result in the death of the patient – must be respected at all times. The point at which death can be declared after loss of circulation and respiration varies and remains widely debated. This is highlighted by the 5-30 minutes no-touch time required in different European countries [7]. Yet, for DCD to be successful, the organs need to be recovered as soon as possible after cardio-respiratory arrest to minimise warm ischaemic damage. Cardio-respiratory criteria have been used extensively by doctors to confirm death for a couple of centuries and are well understood by the public. However, the introduction of DCD programmes and reports of autoresuscitation have highlighted the need for the development of scientifically, ethically and professionally acceptable criteria to diagnose death in time-sensitive situations. It is essential that authoritative legal or professional guidance is available and followed in any country or jurisdiction practising DCD.

There appears to be increasing international consensus that death can be confirmed (and therefore organ recovery can begin) after a minimum of 5 min of continuous cardio-respiratory arrest because this means that the possibility for spontaneous resumption of the circulation has passed [122]. If any circulatory or respiratory activity occurs during these 5 min, then the timing should be started again at the next point of cardio-respiratory arrest. The absence of circulation must be confirmed by the absence of pulsatile flow on an arterial line or by absence of blood flow through the aortic valve on transoesophageal

Figure 12.8. **Diagnosis of death in controlled donation after circulatory death**



Point A = Start of cardio-respiratory arrest; Point B = Permanent loss of circulation; Point C = Irreversible loss of circulation. WLST: Withdrawal of life-sustaining therapies.

echocardiography, on the rare occasions when this is used. Although asystole is not required to determine death, if only an ECG is used to assess the absence of circulation, then asystole must be observed for a minimum of 5 min. Many would consider palpation of a pulse as inadequate in this setting. The diagnosis of death must be made by experienced clinicians not involved in the recovery or transplant process.

The time of 5 min is based on the concept of 'permanent' loss of circulation, i.e. circulation will not be restored, rather than the concept of 'irreversible' loss of circulation, which is more variable and dependent on the available technologies [46]. All human death can be considered to be brain-based. Brain function is lost very quickly after loss of the circulation, which can be viewed simply as a predictor of permanent loss of all brain function once the time for autoresuscitation has passed. If no interventions are undertaken that can restore cerebral perfusion then the same time point will mark the irreversible loss of all brain functions [123]. It follows that diagnosing death at 5 min is conditional on there being no intention to resume CPR or to introduce interventions that may potentially restore cerebral perfusion after the declaration of death (see Figure 12.8). This does not preclude the use of organ-reperfusion techniques since they are applied after the isolation of the cerebral circulation. Techniques to allow *in situ* NRP of both abdominal and thoracic organs while maintaining the principle of permanence in death declaration have been reported recently [121].

During the process of determination of death, preservation and organ recovery, respect for the dying donor and their family must be ensured. At each step, their privacy and dignity must be maintained and the end-of-life wishes of the donor and family must be honoured as far as possible. All personnel involved should make an effort to personalise care within the given time constraints.

12.3.7. Preservation and organ recovery

12.3.7.1. *Pre-recovery preparations*

The surgical team should arrive at the donor hospital before WLST. Upon arrival, the lead surgeon should check the relevant paperwork with the donor co-ordinator (blood group, relevant past medical history, virology and consent for deceased donation) and confirm the time for WLST. This should allow time for preparation of the bench and the operative table, to enable a swift procedure. A team brief is mandatory, particularly when both thoracic and abdominal teams are present, and it allows a common strategy to be agreed to ensure safe organ recovery. The team should be scrubbed in theatre at the time of WLST.

12.3.7.2. *Definitions of warm ischaemia times*

The outcome of transplantation with organs from cDCD donors is significantly influenced by the length of WIT. Following WLST, several time periods have been defined (see Figure 12.6). Note that anastomosis time in the recipient is not included in any of these definitions:

a. Withdrawal time (agonal phase): the time from WLST to circulatory arrest.
b. Asystolic time (First/primary WIT): the time from circulatory arrest to the start of *in situ* preservation.
c. Functional warm ischaemia time (FWIT): the time between the onset of sustained significant hypoperfusion (the start of which depends on national guidelines) and the start of *in situ* preservation [124].
d. Withdrawal to perfusion time (Donor WIT) = Withdrawal time (agonal phase) + Asystolic time (First WIT), sometimes referred to as Total WIT in some countries.

The moment that defines the start of functional warm ischaemia time (significant hypoperfusion) is yet to be universally agreed upon, but in general a sustained fall in systolic blood pressure ≤ 50 or 60 mmHg is accepted in Europe, while a fall in systolic blood pressure < 80 mmHg and/or O_2 saturation < 80 % is accepted in the United States [46, 125]. In addition, in the United States the term Donor WIT refers to the withdrawal-to-perfusion time (total WIT), whereas in the United Kingdom and the Netherlands it refers to the asystolic time (First WIT). Because of these varying definitions being used to describe WIT it is essential to verify the exact definition when comparing literature.

The acceptable FWIT varies for different organs and ranges from 30 min for the liver and heart, to 60 min for the pancreas and lungs and up to 120 min for kidneys [8]. There is a lack of evidence supporting these times, and several reports suggest that longer times yield transplantable organs, especially for kidneys [114, 126] and pancreas [127]. In liver transplantation it has been shown that every minute of extra ischaemia (asystolic WIT) decreases graft survival, with a significantly higher chance of biliary complications [128], and care should be taken when asystolic WIT exceeds 25 min [74]. These times are likely to change with the use of NRP or *ex situ* machine perfusion.

Table 12.4. **Categorisation of the cDCD liver donor**

	Standard cDCD donor	Expanded cDCD donor
Age (years)	< 50	> 50
Weight (kg)	< 100	> 100
ICU stay (days)	< 5	> 5
WIT (min)	≤ 20	20-30
CIT (hours)	≤ 8	> 8-12
Steatosis (%)	≤ 15	> 15
Recommendation	All potential liver donors fulfilling these criteria should be used	These grafts should be used selectively

CIT: cold ischaemia time; DCD: donation after circulatory death; ICU: intensive care unit; WIT: warm ischaemia time.

Following WLST, the donor co-ordinator must communicate the vital signs (saturation, pulse and blood pressure) and inform the procurement team when certain values or time points are met.

12.3.8. Continuous evaluation

The evaluation of cDCD donors starts with a detailed medical and socio-demographic history, which the donor co-ordinator should obtain from all relevant sources (notes, interviews with treating physicians, general practitioners, family etc.). Factors such as age, duration of hospital and ICU admission, the use of high-dose vasopressors and the absence/presence of infection are highly relevant for the decision on whether to utilise the organs.

Based on these characteristics, the 'ideal' cDCD donor can be defined as a donor of age < 50 years with a weight < 100 kg, a short ICU stay (< 5 days) and a WIT < 20 min [46].

The absolute contraindications to cDCD organ donation are the same as those for DBD (see Chapter 7), e.g. invasive or haematological malignancy, untreated systemic infection and prion disease.

Biochemistry samples must be obtained prior to donation and, if relevant, compared with other samples taken before or during admission. The lead surgeon must assess the quality of the perfusion and the aspect and anatomy of the organs *in situ* and on the bench. Unlike DBD, where assessment includes a period before circulatory arrest, DCD assessment is much more difficult and subjective, and it depends on a surgeon's experience.

The decision to utilise cDCD organs should also take into account the recovery factors, such as duration of WIT (withdrawal time, asystolic time, FWIT or withdrawal-to-perfusion time).

NRP offers the additional benefit of in-depth *in situ* macroscopic assessment of the organ's appearance, including the appearance of the small bowel and gall-bladder mucosa (both highly sensitive to ischaemic damage). This is corroborated by serial biochemical and blood gas analyses which are undertaken (every 20-30 min) to evaluate function. Given the limited data available, further work is required to clarify which factors are important.

The use of novel preservation and end-ischaemic perfusion strategies can offer additional options for functional organ assessment, particularly if undertaken at normothermic temperatures. However, the criteria for organ assessment require further refinement and validation.

12.3.9. Organ-specific evaluation criteria

Once a patient's suitability to donate has been established, additional evaluation criteria come into consideration for specific organs. These may relate to the donor's age, the timings of organ recovery (such as agonal phase duration, length of the First WIT or length of predicted CIT) and specific pre-existent co-morbidity (such as cardiovascular disease, hypertension, diabetes and liver disease).

12.3.9.1. *Kidney evaluation criteria*

The absolute contraindications for cDCD kidney transplantation are end-stage kidney disease (chronic kidney disease stage 5, eGFR < 15 mL/min), chronic kidney disease stage 4 (eGFR 15-30 mL/min) or acute cortical necrosis on pre-implantation kidney biopsy [46].

Acute kidney injury, even when requiring dialysis, does not exclude donation but is associated with a higher incidence of DGF (see Chapter 7, §7.2.1).

In addition to donor and recovery issues, factors such as hypertension and cardiovascular disease may have an impact on the outcomes of cDCD kidney transplantation. For these donors, a pre-implantation biopsy may be helpful in identifying those organs that will have a poor outcome when transplanted as a single organ, allowing dual transplantation to be considered [129, 130].

The use of kidneys with prolonged FWIT in excess of 2 h should be restricted to centres investi-

gating *ex situ* perfusion technologies that may enable further evaluation of viability [131], but the criteria remain to be defined. The use of *ex situ* hypothermic machine perfusion has led to the development of viability assessment criteria such as flow on the machine and the level of intracellular enzymes such as glutathione S-transferase, ALT, fatty acid-binding protein [131]. None of the perfusion-pressure dynamic characteristics, the perfusate-effluent biochemical analysis or kidney-transplant biopsy scoring systems – alone or in combination – have sufficient predictive value to justify discard of an organ [132].

12.3.9.2. *Liver evaluation criteria*

The presence of end-stage liver disease, acute liver failure (viral or drug-related) or non-recovering acute liver injury are absolute contraindications for liver donation. The following specific factors should be considered for cDCD liver evaluation:

a. Age – Despite increased utilisation of older cDCD donors, reports suggest that donor age is associated with an increased risk of complications such as graft loss and ITBL [74, 133]. In fact, apart from DCD itself, age is the highest predictor of outcome after liver transplantation [72, 75]. It has been suggested that NRP and/or *ex situ* machine perfusion can help to raise acceptable donor age with good results in cDCD liver transplantation [86].

b. Body mass index – Increased body mass index appears to be associated with higher recipient mortality and a higher risk of graft loss [134-135].

c. FWIT – There is evidence that a time longer than 20 min is associated with poorer outcome, particularly with regard to the development of ITBL [136].

d. Asystolic time – A short asystolic time (< 10 min) is beneficial for graft function [137, 138], and care should be taken when exceeding 25 min [76] unless consideration is given to using NRP.

e. Cold ischaemia time (CIT) – A short CIT (ideally less than 6-8 h) is preferred for cDCD. Longer CIT is associated with increased risk of graft failure, patient mortality and ITBL [139].

f. Based on these considerations, the 2013 United Kingdom guidelines describe the ideal cDCD and the extended criteria cDCD for liver donation, and make recommendations for their use (see Table 12.4 [46]).

Currently, there are no defined criteria for assessing the quality of the graft but, in addition to the factors listed above, macrovesicular steatosis (> 60 %) is probably the best indicator of poor quality, especially when combined with a prolonged FWIT and CIT > 12 h, given the high susceptibility to warm and cold ischaemic injuries.

The use of NRP and/or *ex situ* machine perfusion allows a more detailed evaluation of the liver's function and quality. This evaluation involves the macroscopic aspect before and during NRP perfusion, as well as post-cold-perfusion appearance, the level of bile production, an improving lactate on serial measurements and the liver function test evolution. A dramatic increase in the ALT/AST value is probably an indication not to utilise the liver. Nevertheless, clarification of the liver function test range that would preclude transplantation is needed. Initial experiences with uDCD criteria in Spain [25, 28] suggested that the initial ALT/AST should be < 3 times the upper limit of normal and that during NRP the ALT/AST should not rise to more than four times the upper limit of normal at the end of the procedure. However, this experience in uDCD cannot necessarily be extrapolated to cDCD practice. For example, United Kingdom centres use both an absolute rise < 10 × the upper limit of normal and a trend showing a rapid increase in ALT/AST as contraindications to transplantation.

12.3.9.3. *Pancreas evaluation criteria*

Similarly to cDCD liver grafts, utilisation of the pancreas is more restrictive in cDCD, with a lower donor age and body mass index (< 28 kg/m^2). FWIT is preferably kept as short as possible, although no strong recommendation on an exact limit exists in the literature. Currently the best way to describe pancreas graft quality is by the Pancreas Donor Risk Index, which has been validated in the United Kingdom [140] and in the Eurotransplant region [141]. However, pancreas evaluation and graft assessment also rely heavily on the quality of perfusion, the degree of fatty infiltration, the texture of the graft and possible surgical injury [142]. Nonetheless, the quality of perfusion and especially the interpretation of the degree of fatty infiltration are highly subjective, and the final decision should be made by the pancreas transplantation surgeon.

Based on the donor criteria, the United Kingdom cDCD guidelines [46] suggest classification and graft utilisation as shown in Table 12.5.

Pancreas grafts that are not used for solid organ transplantation should be considered for islet transplantation, particularly when CIT is < 8 h and body mass index is high. Early outcome after cDCD islet transplantation is encouraging and seems com-

parable to DBD islet transplantation [143-145]. Please refer to the latest edition of the Council of Europe *Guide to the quality and safety of tissues and cells for human application*.

12.3.9.4. *Lung evaluation criteria*

cDCD lung donation should be considered in donors aged < 65 years old without pre-existent trauma or lung or pleural disease. Most cDCD lungs can be transplanted without separate *ex situ* assessment. *Ex situ* normothermic machine perfusion should be considered

- when oxygenation is impaired (systemic arterial PO_2 < 40 kPa (300 mmHg) on 100 % FiO_2 and 5 cmH_2O PEEP)
- when a bronchoscopy shows inflammation/soiling of the airway or
- when there is a sustained peak airway pressure of > 30 cmH_2O.

Additional indications for using *ex situ* normothermic perfusion include a smoking history of over 20 pack years, an ICU stay of more than 5 days, an abnormal chest X-ray, withdrawal-to-perfusion time > 60 min to > 90 min for cDCD donors, difficult-to-recruit atelectasis in the donor, an unsatisfactory deflation test on disconnecting endotracheal tube, unsatisfactory palpation of the lungs identifying undetermined masses, nodules or gross oedema, unsatisfactory inspection of the lung after administration of the preservation flush and logistical reasons that will extend donor lung ischaemic time > 10-12 h [46]. *Ex situ* normothermic perfusion assesses the ability of the lung to provide perfusate oxygenation, together with evaluation of the lung compliance, airway resistance and peak airway pressures at a given tidal volume.

12.3.9.5. *Heart evaluation criteria*

The assessment of the cDCD donor heart varies, depending on the procurement approach:

a. DPP: a transthoracic echocardiogram is obtained before WLST to describe ventricular and cardiac valvular function. It is then inspected on the perfusion rig, the manufacturers of which recommend serial measurement of perfusion fluid lactate levels. It is accepted that a downward trend and a reduction between arterial and venous lactates is suggestive of good heart function.

b. TA-NRP: the heart is inspected after return of sinus rhythm within the cDCD donor after weaning off NRP relying on the heart to perfuse the thoracic and abdominal organs. The donor is effectively now a heart-beating donor. The donor heart is assessed clinically and by pulmonary artery catheter (cardiac output and atrial filling pressures), transoesophageal echocardiography and visual inspection. It is also assessed by its ability to support the limited thoraco-abdominal circuit.

12.4. DCD after euthanasia and after medical assistance in dying

For legal reasons, DCD after euthanasia is practised only in the very few countries in the world that allow this practice. This section acknowledges the possibility of DCD after euthanasia in those countries, and its likely introduction in some others, and briefly describes how it is managed. Both Belgium and the Netherlands have laws and national guidance for DCD after euthanasia [146-148]. In 2018 DCD after euthanasia accounted for 9 % of all DCD in Belgium and 7 % of all DCD donors in the Netherlands. In Belgium these donors represented 0.3 % of all euthanasia cases that year [149]. In Canada the practice is termed organ donation after MAID, and guidance for policy has been published [11]. In Canada, donation after MAID has been undertaken successfully in 30 individuals, who donated a total of 74 organs by January 2019 [150].

Individuals requesting euthanasia are never approached for organ donation by their general practitioner, other physicians or the organ donation services. The request for organ donation must only come from the mentally competent individuals themselves. After euthanasia is approved, information can be given about organ donation. The general practitioner will contact the donation services so that a donor co-ordinator can meet the individual to discuss the combination of euthanasia with organ donation and answer all their questions. The organ donor register is checked and if an objection is registered this can be overruled by witnessed, written consent signed by the individual. The physician in charge will always explain that the individual can reverse their decision regarding organ donation until the last second before euthanasia. Euthanasia is not considered to be a natural cause of death in some countries and judicial consent may also be required for organ donation to proceed.

When the individual has consented to organ donation, the process of euthanasia is usually undertaken in the ICU. Intra-arterial monitoring is established *ante mortem* to allow death to be confirmed in

the normal manner, observing the relevant no-touch period for the jurisdiction. Following the declaration of death, the organ recovery process is the same as for cDCD (Category III). The outcomes for transplants performed using organs retrieved after euthanasia are limited. Preliminary data from Belgium suggest good post-transplant graft function and good early recipient outcome in those receiving liver or lung transplants from donors after euthanasia [151, 152].

12.5. Paediatric DCD

The aspects of DCD in the paediatric patient population that differ from those described here for adults are addressed in Chapter 14, Paediatric donation.

12.6. Establishing a hospital cDCD programme

The introduction of cDCD within a hospital needs to be carefully planned to ensure that the various issues and potential obstacles that may be expected and encountered are addressed beforehand. Each hospital should develop its own protocol that is not just based on national legal, ethical and professional guidance, but also addresses local circumstances that influence the logistics and practicalities of cDCD [103, 124, 153]. Those developing the local protocol need to remain aware of the sensitivities of clinical staff in the ICU and in the operating theatres, many of whom are particularly uncomfortable at the interface between end-of-life care and organ donation [151]. The key steps in establishing a hospital programme can be summarised as follows [152]:

a. Establish a team to plan and oversee the implementation of the cDCD programme. This should include representatives from the ICU and Emergency Medicine medical and nursing staff, the local transplant centre, the donor co-ordinators, the theatre staff and the neurosciences team.

b. The ICU must have a policy for WLST. This should be developed and implemented locally by the ICU team, working with the wider multidisciplinary team and adhering to national guidelines or legislation.

c. Establish criteria for referral to the donation services. This is usually whenever a decision on WLST is being considered, irrespective of whether the primary diagnosis is neurological or not. Adopt a whole-hospital approach because some potential DCD donors will be outside the ICU [12].

d. Audit the potential for cDCD in the hospital. This should focus on patients having WLST with no contraindications to donation who die within the timeframe that allows cDCD to proceed. This allows the various departments to plan for the workload.

e. Discuss the practical, moral and ethical issues. It is only once these issues have been addressed and resolved that a protocol for local implementation should be developed.

f. Design a protocol for local implementation. This should be based on the discussion of the team and should address the process of reaching a decision on WLST, triggers for referral, when to inform the judicial services, how and when to approach the family, which *ante mortem* interventions are acceptable, the timing, method and location of WLST, organisation of the operating theatres, criteria for standing down the retrieval team, how death is confirmed and by whom, care of the family after death has been confirmed, arrangements for the patient and family if the retrieval team is stood down, and which *post mortem* interventions are acceptable.

Table 12.5. **Categorisation of the cDCD pancreas donor**

	Standard cDCD donor	Expanded cDCD donor
Age (years)	< 45	45-60
BMI (kg/m^2)	< 28	28-30
WIT (min)	≤ 30	> 30
CIT (hours)	≤ 9	> 9
Steatosis	None	Mild to moderate
Recommendation	All potential pancreas donors fulfilling these criteria should be used	These grafts should be used selectively
	All potential liver donors fulfilling these criteria should be used	

BMI: body mass index; CIT: cold ischaemia time; DCD: donation after circulatory death; WIT: warm ischaemia time.

g. Ensure end-of-life care is not compromised. The quality of end-of-life care and palliative care must remain the highest priority throughout all the steps of the cDCD pathway, wherever the patient is being cared for.

h. Review the early cases (at the start of a new cDCD programme) because this allows any concerns or issues to be addressed and the local protocol to be updated as necessary. Once the programme is embedded, occasional debriefs for the ICU and theatre team are useful after difficult or emotive cases or to highlight particular issues.

i. Establish regular training. This should be targeted at all healthcare staff involved in the cDCD pathway.

12.7. Conclusion

The field of DCD is rapidly evolving, with an increasing number of countries participating in this type of deceased donation. Criteria for donor selection are expanding at the same time as the results of DCD transplants are becoming more favourable. Current developments of *in situ* and *ex situ* organ-preservation techniques may contribute to a greater use of organs per donor, better quality of organs and improved post-transplant outcomes.

DCD is a much-needed addition to DBD when we consider the persisting worldwide shortage of donor organs and the need for countries to progress towards self-sufficiency in transplantation. Moreover, in the overall best interests of the dying patients, there is a need to develop DCD programmes that allow donation in all circumstances of death. However, DCD should not be a substitute for DBD because there still is a higher chance of a poorer outcome after DCD, which is likely due to the extra warm ischaemia in the donor and fewer donated organs per donor.

It is essential that countries considering introducing DCD programmes establish a robust legal, ethical and professional framework to underpin the practice to protect patients, the public and professionals involved in the practice of DCD. Existing programmes should continue to develop by adopting the most recent evidence-based advances in the field.

Research agenda

From the literature and discussion of the available evidence, several topics were identified for which evidence is inconsistent, insufficient or non-existent. For the benefit of patients undergoing transplant procedures, the authors of this guide recommend that future research, where possible in well-designed RCTs, should focus on these research gaps:

1 Defining an evidence-based 'warm ischaemia time' that predicts meaningful transplant outcomes (graft function and survival, organ discards).
2 Continued search for an accurate model of predicting time to death after WLST.
3 Comparison of indications, outcomes and cost-effectiveness of *in situ v. ex situ* organ-perfusion technologies.
4 Identifying accurate, reproducible biochemical and other criteria that guide whether specific organs are utilised or discarded.
5 Document which *ante mortem* interventions are associated with better transplant outcomes for each organ.

12.8. References

1. Kootstra G, Daemen JH, Oomen AP. Categories of non-heart-beating donors. *Transplant Proc* 1995;27: 2893-4.
2. Thuong M, Ruiz A, Evrard P *et al.* New classification of donation after circulatory death donors definitions and terminology. *Transpl Int* 2016;29(7):749-59.
3. American Heart Association. Highlights of the 2019 focused updates to the American Heart Association Guidelines for cardiopulmonary resuscitation and emergency cardiovascular care, available at https://eccguidelines.heart.org/wp-content/uploads/2019/11/2019-Focused-Updates_Highlights_EN.pdf, accessed: 20/02/2020.
4. Merchant RM, Topjian AA, Panchal AR *et al.* Part 1: Executive Summary: 2020 American Heart Association Guidelines for cardiopulmonary resuscitation and emergency cardiovascular care. *Circulation* 2020; 142(16_suppl_2):S337-S357. https://doi.org/10.1161/CIR.0000000000000918.
5. Perkins GD, Graesner J-T, Semeraro F *et al.* European Resuscitation Council Guidelines 2021: Executive summary. *Resuscitation* 2021 Apr;161:1-60. https://doi.org/10.1016/j.resuscitation.2021.02.003.
6. International figures on donation and transplantation – 2018. *Newsletter Transplant* 2019;24: available at https://freepub.edqm.eu/publications/NT-archive/detail, accessed 2 March 2022.
7. Lomero M, Gardiner D, Coll E *et al.* Donation after circulatory death today: an updated overview of the European landscape. *Transpl Int* 2020 Jan;33(1):76-88. https://doi.org/10.1111/tri.13506.
8. Smith M, Dominguez-Gil B, Greer DM *et al.* Organ donation after circulatory death: current status and future potential. *Intensive Care Med* 2019 Mar;45(3): 310-21. https://doi.org/10.1007/s00134-019-05533-0.
9. Ysebaert D, Van Beeumen G, De Greef K *et al.* Organ

procurement after euthanasia: Belgian experience. *Transplant Proc* 2009;41:585-6.

10. Bollen J, de Jongh W, Hagenaars J *et al.* Organ donation after euthanasia: a Dutch practical manual. *Am J Transplant* 2016;16(7):1967-72.
11. Downar J, Shemie SD, Gillrie C *et al.* Deceased organ and tissue donation after medical assistance in dying and other conscious and competent donors: guidance for policy. *CMAJ* 2019 Jul 2;191(26):E745. https://doi.org/10.1503/cmaj.190724. Full guidance available at www.cmaj.ca/content/cmaj/suppl/2019/05/27/191.22.E604.DC1/181648-guide-1-at.pdf, accessed 30 June 2021.
12. Manara A, Procaccio F, Domínguez-Gil B. Expanding the pool of deceased organ donors: the ICU and beyond. *Intensive Care Med* 2019;45:357-60. DOI: 10.1007/s00134-019-05546-9.
13. Manara A, Domínguez-Gil B. Controlling the uncontrolled: can we realise the potential of uncontrolled donation after circulatory death? *Resuscitation* 2019;137:234-6. https://doi.org/10.1016/j.resuscitation.2019.02.010.
14. Domínguez-Gil B, Duranteau J, Mateos A *et al.* Uncontrolled donation after circulatory death: European practices and recommendations for the development and optimization of an effective programme. *Transpl Int* 2016;29(8):842-59.
15. Sánchez-Fructuoso AI, Pérez-Flores I, Del Río F *et al.* Uncontrolled donation after circulatory death: a cohort study of data from a long-standing deceased-donor kidney transplantation program. *Am J Transplant* 2019;19(6):1693-1707.
16. Molina M, Guerrero-Ramos F, Fernández-Ruiz M *et al.* Kidney transplant from uncontrolled donation after circulatory death donors maintained by nECMO has long term outcomes comparable to standard criteria donation after brain death. *Am J Transplant* 2019;19(2):434-47.
17. Demiselle J, Augusto JF, Videcoq M *et al.* Transplantation of kidneys from uncontrolled donation after circulatory determination of death: comparison with brain death donors with or without extended criteria and impact of normothermic regional perfusion. *Transpl Int* 2016;29(4):432-42.
18. Peters-Sengers H, Homan van der Heide JJ, Heemskerk MB *et al.* Similar 5-year estimated glomerular filtration rate between kidney transplants from uncontrolled and controlled donors after circulatory death – a Dutch cohort study. *Transplantation* 2017;101(6):1144-51.
19. Delsuc C, Faure A, Berthiller J *et al.* Uncontrolled donation after circulatory death: comparison of two kidney preservation protocols on graft outcomes. *BMC Nephrol* 2018;19(1):3.
20. Del Río F, Andrés A, Padilla M *et al.* Kidney transplantation from donors after uncontrolled circulatory death: the Spanish experience. Spanish Group for the Study of Donation after Circulatory Death. *Kidney Int* 2019 Feb;95(2):420-8. https://doi.org/10.1016/j.kint.2018.09.014.
21. Antoine C, Savoye E, Gaudez F *et al.* Kidney transplant from uncontrolled donation after circulatory death: contribution of normothermic regional perfusion. *Transplantation* 2020 Jan;104(1):130-6. https://doi.org/10.1097/TP.0000000000002753.
22. ONT (Organización Nacional de Trasplantes). Spanish annual reports on donation and transplantation from donation after circulatory death organ donors, available at www.ont.es/infesp/Paginas/Memorias.aspx, accessed 30 June 2021.
23. Georgiades F, Hosgood SA, Butler AJ, Nicholson ML. Use of *ex vivo* normothermic machine perfusion after normothermic regional perfusion to salvage a poorly perfused DCD kidney. *Am J Transplant* 2019 Dec;19(12):3415-19.
24. Hosgood SA, Thompson E, Moore T *et al.* Normothermic machine perfusion for the assessment and transplantation of declined human kidneys from donation after circulatory death donors. *Br J Surg* 2018 Mar;105(4):388-94.
25. De Carlis R, Di Sandro S, Lauterio A *et al.* Successful donation after cardiac death liver transplants with prolonged warm ischemia time using normothermic regional perfusion. *Liver Transpl* 2017;23(2):166-73.
26. Savier E, Dondero F, Vibert E *et al.* First experience of liver transplantation with type 2 donation after cardiac death in France. *Liver Transpl* 2015;21(5):631-43.
27. Fondevila C, Hessheimer AJ, Ruiz A *et al.* Liver transplant using donors after unexpected cardiac death: novel preservation protocol and acceptance criteria. *Am J Transplant* 2007;7(7):1849-55.
28. Fondevila C, Hessheimer AJ, Flores E *et al.* Applicability and results of Maastricht type 2 donation after cardiac death liver transplantation. *Am J Transplant* 2012;12(1):162-70.
29. Suarez F, Otero A, Solla M *et al.* Biliary complications after liver transplantation from Maastricht category-2 non-heart-beating donors. *Transplantation* 2008;85(1):9-14.
30. Otero A, Gómez-Gutiérrez M, Suarez F *et al.* Liver transplantation from Maastricht category 2 non-heart-beating donors. *Transplantation* 2003;76(7):1068-73.
31. Quintela J, Gala B, Baamonde I *et al.* Long-term results for liver transplantation from non-heart-beating donors maintained with chest and abdominal compression-decompression. *Transplant Proc* 2005;37(9):3857-8.

32. Jiménez-Galanes S, Meneu-Diaz MJ, Elola-Olaso AM *et al.* Liver transplantation using uncontrolled non-heart-beating donors under normothermic extracorporeal membrane oxygenation. *Liver Transpl* 2009;15(9):1110-18.
33. Jiménez-Romero C, Manrique A, Calvo J *et al.* Liver transplantation using uncontrolled donors after circulatory death: a 10-year single-center experience. *Transplantation* 2019;103(12):2497-2505.
34. Blasi A, Hessheimer AJ, Beltrán J *et al.* Liver transplant from unexpected donation after circulatory determination of death donors: a challenge in perioperative management. *Am J Transplant* 2016;16(6):1901-8.
35. de Antonio DG, Marcos R, Laporta R *et al.* Results of clinical lung transplant from uncontrolled non-heart-beating donors. *J Heart Lung Transplant* 2007;26(5): 529-34.
36. Gómez de Antonio D, Campo-Cañaveral JL, Crowley S *et al.* Clinical lung transplantation from uncontrolled non-heart-beating donors revisited. *J Heart Lung Transplant* 2012;31(4):349-53.
37. Gámez P, Díaz-Hellin V, Marrón C *et al.* Development of a non-heart-beating lung donor program with 'bithermia preservation', and results after one year of clinical experience. *Arch Bronconeumol* 2012;48(9): 338-41.
38. Valenza F, Citerio G, Palleschi A *et al.* Successful transplantation of lungs from an uncontrolled donor after circulatory death preserved *in situ* by alveolar recruitment maneuvers and assessed by *ex vivo* lung perfusion. *Am J Transplant* 2016;16(4):1312-18.
39. Valdivia D, Gómez de Antonio D, Hoyos L *et al.* Expanding the horizons: uncontrolled donors after circulatory death for lung transplantation – first comparison with brain death donors. *Clin Transplant* 2019 Jun;33(6):e13561.
40. Watanabe Y, Healey A, Scott M *et al.* Initial experience with non-perfused organ donors for lung transplantation. *J Heart Lung Transplant*. 2019;38(4):S190.
41. Coll E, Miñambres E, Sánchez-Fructuoso A *et al.* Uncontrolled donation after circulatory death: a unique opportunity. *Transplantation* 2020 Aug;104(8):1542-52. https://doi.org/10.1097/TP.0000000000003139.
42. Manara AR, Dominguez-Gil B, Perez Villares JM, Soar J. What follows refractory cardiac arrest: death, extra-corporeal cardiopulmonary resuscitation (E-CPR), or uncontrolled donation after circulatory death? *Resuscitation* 2016;108:A3-A5. https://doi.org/10.1016/j.resuscitation.2016.08.028.
43. Roncon-Albuquerque R Jr, Gaião S, Figueiredo P *et al.* An integrated program of extracorporeal membrane oxygenation (ECMO) assisted cardiopulmonary resuscitation and uncontrolled donation after circulatory determination of death in refractory cardiac arrest. *Resuscitation* 2018;133:88-94.
44. Bernat JL, Capron AM, Bleck TP *et al.* The circulatory-respiratory determination of death in organ donation. *Crit Care Med* 2010;38(3):963-70.
45. Shemie SD, Baker AJ, Knoll G *et al.* National recommendations for donation after cardiocirculatory death in Canada: donation after cardiocirculatory death in Canada. *CMAJ* 2006;175(8):S1.
46. British Transplantation Society. United Kingdom guidelines: transplantation from donors after deceased circulatory death, July 2013, available at https://bts.org.uk/wp-content/uploads/2016/09/15_BTS_Donors_DCD-1.pdf, accessed 30 June 2021.
47. Graham S, Tooley A, Huckson S *et al.* National Health and Medical Research Council, Australian Organ and Tissue Donation and Transplantation Authority, Australian Government, Organ and Tissue Authority. National protocol for donation after cardiac death, 2010, available at https://donatelife.gov.au/sites/default/files/DCD%20protocol%20020311-0e4e2c3d-2ef5-4dff-b7ef-af63d0bf6a8a-1.PDF, accessed 30 June 2021.
48. Munjal KG, Wall SP, Goldfrank LR *et al.* A rationale in support of uncontrolled donation after circulatory determination of death. *Hastings Cent Rep* 2013;43(1): 19-26.
49. Bernat JL. Determining death in uncontrolled DCDD organ donors. *Hastings Cent Rep* 2013;43(1):30-3.
50. Bernat JL, Bleck TP, Blosser SA *et al.* Circulatory death determination in uncontrolled organ donors: a panel viewpoint. *Ann Emerg Med* 2014;63(4):384-90.
51. Matesanz R, Coll E, Domínguez-Gil B. Response to circulatory death determination in uncontrolled organ donors: a panel viewpoint. *Ann Emerg Med* 2014;63(1):87-9.
52. Kerforne T, Allain G, Giraud S *et al.* Defining the optimal duration for normothermic regional perfusion in the kidney donor: a porcine preclinical study. *Am J Transplant* 2019 Mar;19(3):737-51.
53. Oniscu GC, Siddique A, Dark J. Dual temperature multi-organ recovery from a Maastricht category III donor after circulatory death. *Am J Transplant* 2014; 14:2181-6.
54. Suárez F, Otero A, Solla M *et al.* Biliary complications after liver transplantation from Maastricht category-2 non-heart-beating donors. *Transplantation* 2008; 85(1):9-14.
55. Valero R, Cabrer C, Oppenheimer F *et al.* Normothermic recirculation reduces primary graft dysfunction of kidneys obtained from non-heart-beating donors. *Transpl Int* 2000;13:303-10.
56. Reznik ON, Skvortsov AE, Reznik AO *et al.* Uncontrolled donors with controlled reperfusion after

sixty minutes of asystole: a novel reliable resource for kidney transplantation. *PLoS One* 2013 May 30;8(5): e64209. https://doi.org/10.1371/journal.pone.0064209. Print 2013.

57. Healey A, Watanabe Y, Mills C *et al.* Initial lung transplantation experience with uncontrolled donation after cardiac death in North America. *Am J Transplant* 2020 Jun;20(6):1574-81. https://doi.org/10.1111/ajt.15795.
58. Palleschi A, Tosi D, Rosso L *et al.* Successful preservation and transplant of warm ischaemic lungs from controlled donors after circulatory death by prolonged *in situ* ventilation during normothermic regional perfusion of abdominal organs. *Interact Cardiovasc Thorac Surg* 2019 Nov 1;29(5):699-705. DOI: 10.1093/icvts/ivz160.
59. Pérez-Villares JM, Lara-Rosales R, Gil-Piñero E *et al.* Ethics in approaching families about organ donation from patients in out-of-hospital asystole. *Emergencias* 2016;28:55-61.
60. Molina M, Domínguez-Gil B, Pérez-Villares JM *et al.* Uncontrolled donation after circulatory death: ethics of implementation. *Curr Opin Organ Transplant*. 2019; 24(3):358-63.
61. Manara A. Bespoke end-of-life decision making in ICU: has the tailor got the right measurements? *Crit Care Med* 2015 Apr;43(4):909-10.
62. Sprung CL, Cohen SL, Sjokvist P *et al.* End-of-life practices in European intensive care units: the Ethicus Study. *JAMA* 2003;290(6):790-7.
63. Sprung CL, Ricou B, Hartog CS *et al.* Changes in end-of-life practices in European intensive care units from 1999 to 2016. *JAMA* 2019;322(17):1692-1704. https://doi.org/10.1001/jama.2019.14608.
64. Nelson HM, Glazier AK, Delmonico FL. Changing patterns of organ donation: brain dead donors are not being lost by donation after circulatory death. *Transplantation* 2016 Feb;100(2):446-50. https://doi.org/10.1097/TP.0000000000000954.
65. Broderick AR, Manara A, Bramhall S *et al.* A donation after circulatory death program has the potential to increase the number of donors after brain death. *Crit Care Med* 2016;44:352-9.
66. Rivers J, Manara AR, Thomas I, Derrick E. Impact of a devastating brain injury pathway on outcomes, resources and organ donation: 3 years' experience in a regional neurosciences ICU. *Neurocrit Care* 2020 Aug;33(1):165-72. https://doi.org/10.1007/s12028-019-00879-1.
67. NHS Blood and Transplant. Annual report on the potential donor audit 2018-2019 (2019), available at: https://nhsbtdbe.blob.core.windows.net/umbraco-assets-corp/16878/annual-pda-report-2018-19.pdf, accessed 1 July 2021.
68. Weber M, Dindo D, Demartines N *et al.* Kidney transplantation from donors without a heartbeat. *N Engl J Med* 2002;347(4):248-55.
69. Summers DM, Johnson RJ, Allen J *et al.* Analysis of factors that affect outcome after transplantation of kidneys donated after cardiac death in the UK: a cohort study. *Lancet* 2010;376(9749):1303-11.
70. Summers DM, Watson CJ, Pettigrew GJ *et al.* Kidney donation after circulatory death (DCD): state of the art. *Kidney Int* 2015;88(2):241-9.
71. van Heurn LW, Talbot D, Nicholson ML *et al.* Recommendations for donation after circulatory death kidney transplantation in Europe. *Transpl Int* 2016; 29(7):780-9.
72. Feng S, Goodrich NP, Bragg-Gresham JL *et al.* Characteristics associated with liver graft failure: the concept of a donor risk index. *Am J Transplant* 2006; 6(4):783-90.
73. Braat AE, Blok JJ, Putter H *et al.* The Eurotransplant donor risk index in liver transplantation: ET-DRI. *Am J Transplant* 2012;12(10):2789-96.
74. Jay C, Ladner D, Wang E *et al.* A comprehensive risk assessment of mortality following donation after cardiac death liver transplant – an analysis of the national registry. *J Hepatol* 2011;55(4):808-13.
75. Grewal HP, Willingham DL, Nguyen J *et al.* Liver transplantation using controlled donation after cardiac death donors: an analysis of a large single-center experience. *Liver Transpl* 2009;15(9):1028-35.
76. Fujita S, Mizuno S, Fujikawa T *et al.* Liver transplantation from donation after cardiac death: a single center experience. *Transplantation* 2007;84(1):46-9.
77. Abt PL, Desai NM, Crawford MD *et al.* Survival following liver transplantation from non-heart-beating donors. *Ann Surg* 2004;239(1):87-92.
78. Abt P, Crawford M, Desai N *et al.* Liver transplantation from controlled non-heart-beating donors: an increased incidence of biliary complications. *Transplantation* 2003;75(10):1659-63.
79. Jay CL, Lyuksemburg V, Ladner DP *et al.* Ischemic cholangiopathy after controlled donation after cardiac death liver transplantation: a meta-analysis. *Ann Surg* 2011;253(2):259-64.
80. Blok JJ, Detry O, Putter H *et al.* Long-term results of liver transplantation from donation after circulatory death. *Liver Transpl* 2016;22(8):1107-14.
81. Miñambres E, Suberviola B, Dominguez-Gil B *et al.* Improving the outcomes of organs obtained from controlled donation after circulatory death donors using abdominal normothermic regional perfusion. *Am J Transplant* 2017;17(8):2165-72.
82. Hessheimer AJ, Coll E, Torres F *et al.* Normothermic regional perfusion vs. super-rapid recovery in controlled donation after circulatory death liver

transplantation. *J Hepatol* 2019 Apr;70(4):658-65. https://doi.org/10.1016/j.jhep.2018.12.013.

83. Watson CJE, Hunt F, Messer S *et al.* In situ normothermic perfusion of livers in controlled circulatory death donation may prevent ischemic cholangiopathy and improve graft survival. *Am J Transplant* 2019 Jun; 19(6):1745-58. https://doi.org/10.1111/ajt.15241.
84. Dutkowski P, Polak WG, Muiesan P *et al.* First comparison of hypothermic oxygenated perfusion versus static cold storage of human donation after cardiac death liver transplants: an international-matched case analysis. *Ann Surg* 2015;262(5):764-70.
85. Ravikumar R, Jassem W, Mergental H *et al.* Liver transplantation after *ex vivo* normothermic machine preservation: a phase 1 (first-in-man) clinical trial. *Am J Transplant* 2016;16(6):1779-87.
86. Nasralla D, Coussios CC, Mergental *et al.* Consortium for Organ Preservation in Europe. A randomized trial of normothermic preservation in liver transplantation. *Nature* 2018;557(7703):50-6.
87. Muthusamy AS, Mumford L, Hudson A *et al.* Pancreas transplantation from donors after circulatory death from the United Kingdom. *Am J Transplant* 2012;12(8):2150-6.
88. Salvalaggio PR, Davies DB, Fernandez LA *et al.* Outcomes of pancreas transplantation in the United States using cardiac-death donors. *Am J Transplant* 2006;6(5 Pt 1):1059-65.
89. Shahrestani S, Webster AC, Lam VW *et al.* Outcomes from pancreatic transplantation in donation after cardiac death: a systematic review and meta-analysis. *Transplantation* 2017;101(1):122-30.
90. White CW, Lillico R, Sandha J *et al.* Physiologic changes in the heart following cessation of mechanical ventilation in a porcine model of donation after circulatory death: implications for cardiac transplantation. *Am J Transplant* 2016;16(3):783-93.
91. Van Raemdonck DE, Jannis NC, Rega FR *et al.* Extended preservation of ischemic pulmonary graft by postmortem alveolar expansion. *Ann Thorac Surg* 1997;64(3):801-8.
92. Mason DP, Thuita L, Alster JM *et al.* Should lung transplantation be performed using donation after cardiac death: the United States experience. *J Thorac Cardiovasc Surg* 2008;136(4):1061-6.
93. Van Raemdonck D, Keshavjee S, Levvey B *et al.* Donation after cardiocirculatory death in lung transplantation- five-year follow-up from the ISHLT registry. *J Heart Lung Transplant*. 2019;38:1235-45.
94. Miñambres E, Ruiz P, Ballesteros MA *et al.* Combined lung and liver procurement in controlled donation after circulatory death using normothermic abdominal perfusion. Initial experience in two Spanish centers. *Am J Transplant* 2020 Jan;20(1):231-40.
95. Dhital KK, Iyer A, Connellan M *et al.* Adult heart transplantation with distant procurement and ex-vivo preservation of donor hearts after circulatory death: a case series. *Lancet* 2015;385(9987):2585-91.
96. Messer SJ, Axell RG, Colah S *et al.* Functional assessment and transplantation of the donor heart after circulatory death. *J Heart Lung Transplant* 2016;35(12): 1443-52.
97. Tchana-Sato V, Ledoux D, Detry O *et al.* Successful clinical transplantation of hearts donated after circulatory death using normothermic regional perfusion. *J Heart Lung Transplant* 2019;38(6):593-8.
98. Macdonald P, Dhital K. Heart transplantation from donation-after-circulatory-death (DCD) donors: back to the future – Evolving trends in heart transplantation from DCD donors. *J Heart Lung Transplant* 2019 Jun;38(6):599-600. https://doi.org/10.1016/j.healun.2019.03.010.
99. Murphy P, Boffa C, Manara A *et al.* In-hospital logistics: What are the key aspects for succeeding in each of the steps of the process of controlled DCD. *Transplant Int* 2016;29(7):760-70.
100. Academy of Medical Royal Colleges, Donation Ethics Committee. An ethical framework for controlled donation after circulatory death, 2011, available at www.aomrc.org.uk/reports-guidance/ukdec-reports-and-guidance/ethical-framework-controlled-donation-circulatory-death-full-report/, accessed 1 Jul 2021.
101. General Medical Council. Treatment and care towards the end of life: good practice in decision making, 2010, available at www.gmc-uk.org/guidance/ethical_guidance/end_of_life_decision_making_models.asp, accessed 1 Jul 2021.
102. Cao Y, Shahrestani S, Chew HC *et al.* Donation after circulatory death for liver transplantation: a meta-analysis on the location of life support withdrawal affecting outcomes. *Transplantation* 2016;100(7): 1513-24.
103. Thomas I, Caborn S, Manara AR. Experiences in the development of non-heart beating organ donation scheme in a regional neurosciences intensive care unit. *Br J Anaesth* 2008;100(6):820-6.
104. Leiden H, Haase-Kromwijk B, Hoitsma A, Jansen N. Controlled donation after circulatory death in the Netherlands: more organs, more efforts. *Neth J Med* 2016;74(7):285-91.
105. Kotsopoulos A, Jansen N, Abdo WF. When circulatory death does not come in time in potential organ donors. *Crit Care* 2019 May 2;23(1):154. https://doi.org/10.1186/s13054-019-2443-4.
106. Reid AW, Harper S, Jackson CH *et al.* Expansion of the kidney donor pool by using cardiac death donors

with prolonged time to cardiorespiratory arrest. *Am J Transplant* 2011;11(5):995-1005.

107. Domínguez-Gil B, Coll E, Elizalde J *et al.* for the ACCORD-Spain study group. Expanding the donor pool through intensive care to facilitate organ donation: results of a Spanish multicenter study. *Transplantation* 2017;101(8):e265-e272.
108. NHS Blood and Transplant 2012. Timely identification and referral of potential organ donors, available at: https://nhsbtdbe.blob.core.windows.net/umbraco-assets-corp/1337/timely-identification-and-referral-of-potential-organ-donors-nhsbt.pdf, accessed 1 Jul 2021.
109. Lewis J, Peltier J, Nelson H *et al.* Development of the University of Wisconsin donation After Cardiac Death Evaluation Tool. *Prog Transplant* 2003;13(4): 265-73.
110. DeVita MA, Brooks MM, Zawistowski C *et al.* Donors after cardiac death: validation of identification criteria (DVIC) study for predictors of rapid death. *Am J Transplant* 2008;8(2):432-41.
111. Wind J, Snoeijs MG, Brugman CA *et al.* Prediction of time of death after withdrawal of life-sustaining treatment in potential donors after cardiac death. *Crit Care Med* 2012;40(3):766-9.
112. NHS Blood and Transplant. Approaching the families of potential organ donors. Best practice guidance, 2013, available at https://nhsbtdbe.blob.core.windows.net/umbraco-assets-corp/1462/family_approach_best_practice_guide-1.pdf, accessed 1 Jul 2021.
113. Hulme W, Allen J, Manara AR *et al.* Factors influencing the family consent rate for organ donation in the UK. *Anaesthesia* 2016;71:1053-63. DOI:10.1111/anae.13535.
114. ONT (Organización Nacional de Trasplantes). National protocol on liver donation and transplantation from controlled DCD donors [in Spanish], available at www.ont.es/infesp/DocumentosDeConsenso/PROTOCOLO%20NACIONAL%20DE%20DONACIÓN%20Y%20TRASPLANTE%20HEPÁTICO%20EN%20DONACIÓN%20EN%20ASISTOLIA%20CONTROLADA_Agosto%202015_FINAL.pdf, accessed 1 Jul 2021.
115. Gardiner D, Wind T, Cole B *et al.*; ELPAT Deceased Donation Working Group. European vignettes in donation after circulatory death. *Prog Transplant* 2017 Sep; 27(3):286-90. https://doi.org/10.1177/1526924817715462.
116. Coggon J, Brazier M, Murphy P *et al.* Best interests and potential organ donors. *BMJ* 2008 Jun 14; 336(7657):1346-7.
117. Academy of Medical Royal Colleges, Donation Ethics Committee. Interventions before death to optimise donor organ quality and improve transplant outcomes: guidance [from the UK Donation Ethics Committee], 10 Sep 2014, available at www.aomrc.org.uk/reports-guidance/ukdec-reports-and-guidance/interventions-death-optimise-donor-organ-quality-improve-transplant-outcomes-guidance/, accessed 1 Jul 2021.
118. Department of Health. Organ donation after circulatory death. Report of a consensus meeting: Intensive Care Society, NHS Blood and Transplant and British Transplantation Society, 2010, available at https://nhsbtdbe.blob.core.windows.net/umbraco-assets-corp/1360/donation-after-circulatory-death-dcd_consensus_2010.pdf, accessed 1 Jul 2021.
119. Pérez-Villares JM, Rubio JJ, Del Río F, Miñambres E. Validation of a new proposal to avoid donor resuscitation in controlled donation after circulatory death with normothermic regional perfusion. *Resuscitation* 2017;117:46-9.
120. Donation after controlled circulatory death: National Protocol, available at www.agence-biomedecine.fr/IMG/pdf/v7_guide_ddac_miii_novembre_2019_eng.pdf, accessed 20 July 2021.
121. Manara A, Shemie SD, Large S *et al.* Maintaining the permanence principle for death during *in situ* normothermic regional perfusion for donation after circulatory death organ recovery: a United Kingdom and Canadian proposal. *Am J Transplant* 2020 Aug; 20(8):2017-25. https://doi.org/10.1111/ajt.15775.
122. Gardiner D, Shemie S, Manara A *et al.* International perspective on the diagnosis of death. *Br J Anaesth* 2012;108(Suppl 1):i14-i28.
123. Manara AR. All human death is brain death: the legacy of the Harvard criteria. *Resuscitation* 2019;138:210-12. https://doi.org/10.1016/j.resuscitation.2019.03.011.
124. Manara AR, Murphy PG, O'Callaghan G. Donation after circulatory death. *Br J Anaesth* 2012;108:i108-i121
125. Reich DJ, Mulligan DC, Abt PL *et al.* ASTS recommended practice guidelines for controlled donation after cardiac death organ procurement and transplantation. *Am J Transplant* 2009;9(9):2004-11.
126. Suntharalingam C, Sharples L, Dudley C *et al.* Time to cardiac death after withdrawal of life-sustaining treatment in potential organ donors. *Am J Transplant* 2009;9(9):2157-65.
127. Blok JJ, Ringers J, Schaapherder AF *et al.* Report of the first five DCDD pancreas transplants within the Eurotransplant region; excellent results with prolonged first warm ischemia times. *Transpl Int* 2013; 26(4):e31-e33.
128. Taner CB, Bulatao IG, Perry DK *et al.* Asystole to cross-clamp period predicts development of biliary complications in liver transplantation using donation after cardiac death donors. *Transpl Int* 2012;25(8): 838-46.

129. Remuzzi G, Grinyo J, Ruggenenti P *et al.* Early experience with dual kidney transplantation in adults using expanded donor criteria. Double Kidney Transplant Group (DKG). *J Am Soc Nephrol* 1999;10(12):2591-8.

130. Remuzzi G, Cravedi P, Perna A *et al.* Long-term outcome of renal transplantation from older donors. *N Engl J Med* 2006;354(4):343-52.

131. Talbot D, D'Alessandro A. *Organ donation and transplantation after cardiac death*. ISBN 978-0-19-921733-5. Oxford: Oxford University Press, 2009.

132. Jochmans I, Moers C, Smits JM *et al.*. The prognostic value of renal resistance during hypothermic machine perfusion of deceased donor kidneys. *Am J Transplant* 2011;11(10):2214-20.

133. Mateo R, Cho Y, Singh G *et al.* Risk factors for graft survival after liver transplantation from donation after cardiac death donors: an analysis of OPTN/UNOS data. *Am J Transplant* 2006;6(4):791-6.

134. Chan EY, Olson LC, Kisthard JA *et al.* Ischemic cholangiopathy following liver transplantation from donation after cardiac death donors. *Liver Transpl* 2008;14(5):604-10.

135. Mathur AK, Heimbach J, Steffick DE *et al.* Donation after cardiac death liver transplantation: predictors of outcome. *Am J Transplant* 2010;10(11):2512-19.

136. Lee KW, Simpkins CE, Montgomery RA *et al.* Factors affecting graft survival after liver transplantation from donation after cardiac death donors. *Transplantation* 2006;82(12):1683-8.

137. Rojas-Peña A, Sall LE, Gravel MT *et al.* Donation after circulatory determination of death: the University of Michigan experience with extracorporeal support. *Transplantation* 2014;98(3):328-34.

138. Taner CB, Bulatao IG, Willingham DL *et al.* Events in procurement as risk factors for ischemic cholangiopathy in liver transplantation using donation after cardiac death donors. *Liver Transpl* 2012;18(1):100-11.

139. de Vera ME, Lopez-Solis R, Dvorchik I *et al.* Liver transplantation using donation after cardiac death donors: long-term follow-up from a single center. *Am J Transplant* 2009;9(4):773-81.

140. Mittal S, Lee FJ, Bradbury L *et al.* Validation of the Pancreas Donor Risk Index for use in a UK population. *Transpl Int* 2015;28(9):1028-33.

141. Blok JJ, Kopp WH, Verhagen MJ *et al.* The value of PDRI and P-PASS as predictors of outcome after pancreas transplantation in a large European pancreas transplantation center. *Pancreas* 2016;45(3):331-6.

142. Marang-van de Mheen PJ, Hilling DE, Dirkes MC *et al.* Surgical injuries of pancreatic allografts during procurement. *Clin Transplant* 2011;25(5):737-43.

143. Saito T, Gotoh M, Satomi S *et al.* Islet transplantation using donors after cardiac death: report of the Japan Islet Transplantation Registry. *Transplantation* 2010;90(7):740-7.

144. Zhao M, Muiesan P, Amiel SA *et al.* Human islets derived from donors after cardiac death are fully biofunctional. *Am J Transplant* 2007;7(10):2318-25.

145. Andres A, Kin T, O'Gorman D *et al.* Clinical islet isolation and transplantation outcomes with deceased cardiac death donors are similar to neurological determination of death donors. *Transpl Int* 2016;29(1):34-40.

146. Bollen J, Ten Hoopen R, Ysebaert D *et al.* Legal and ethical aspects of organ donation after euthanasia in Belgium and the Netherlands. *J Med Ethics* 2016;42(8):486-9.

147. Belgian law on Euthanasia (28 May 2002) [in Dutch/French/German], available at www.ejustice.just.fgov.be/cgi_loi/change_lg.pl?language=nl&la=N&table_name=wet&cn=2002052837, accessed 1 July 2021.

148. Dutch Transplant Foundation, Guidelines on Organ donation after euthanasia, version 2, March 2021 [in Dutch], available at www.transplantatiestichting.nl/files/2021-02/richtlijn-orgaandonatie-en-euthanasie-2021.pdf?3b5bf10ba6, accessed 1 July 2021.

149. Belgian Federal Public Service: Health, Food Chain Safety and Environment. Number of euthanasia cases in Belgium [in Dutch], available at https.//overlegorganen.gezondheid.belgie.be/nl/documenten/euthanasie-cijfers-voor-het-jaar-2018, accessed 1 July 2021.

150. Ball IM, Healey A, Keenan S *et al.* Organ donation after medical assistance in dying – Canada's first cases. *N Engl J Med* 2020 Feb 6;382(6):576-7. https://doi.org/10.1056/NEJMc1915485.

151. Gilbo N, Jochmans I, Jacobs-Tulleneers-Thevissen D *et al.* Survival of patients with liver transplants donated after euthanasia, circulatory death, or brain death at a single center in Belgium. *JAMA* 2019;322:78-80. https://doi.org/10.1001/jama.2019.6553.

152. Van Raemdonck D, Verleden GM, Dupont L *et al.* Initial experience with transplantation of lungs recovered from donors after euthanasia. *Applied Cardiopulmonary Pathophysiology* 2011;15(1):38-48, available at www.researchgate.net/publication/228621607_Initial_experience_with_transplantation_of_lungs_recovered_from_donors_after_euthanasia.

153. Haase B, Bos M, Boffa C *et al.* Ethical, legal, and societal issues and recommendations for controlled and uncontrolled DCD. *Transpl Int* 2016 Jul;29(7):771-9.

154. Mandell MS, Zamudio S, Seem D *et al.* National evaluation of healthcare provider attitudes toward organ donation after cardiac death. *Crit Care Med* 2006;34:2952-8.

155. Cain H, Manara AR. Implementing a controlled

(Maastricht 3) DCD programme – a UK perspective.
Organs Tiss Cells 2012;15:171-8.

Related material

Appendix 23. Donation after circulatory death – reporting form (Belgium, English-language version)
Appendix 24. Donation after circulatory death – reporting form (Netherlands, English-language version)

Chapter 13. **Living donation**

13.1. Introduction

In 2010, through the Madrid Resolution, countries were urged to pursue self-sufficiency in transplantation, i.e. to satisfy the transplant needs of their patients by using resources from within their own patient population. The key to self-sufficiency is developing donation from deceased donors (DDs) to its maximum therapeutic potential by facilitating donation, maximising the outcomes from each donor and optimising the results of transplantation. Nevertheless, living donation has become a necessary addition if countries are to achieve self-sufficiency and is therefore increasingly performed in Europe. Thus, deceased donation and living donation should be regarded as complementary sources of organs for transplant [1].

From an ethical, medical, psychosocial and surgical point of view, it should be emphasised that living donation presents some unique considerations:

a. The living donor (LD) is not a patient – is not suffering from an illness – but on the contrary is a healthy person who is selected for donation on the basis of their health. It is hard to evaluate the long-term implications of donating an organ during a person's lifetime, because the optimal control group from the general population is difficult to identify and validate [2, 3].

b. The surgical procedure is not performed with the aim of removing a malfunctioning, infected or cancerous organ, but rather an optimally functioning one.

c. Social and healthcare insurance systems have not been conceived with living donation in mind.

Worldwide, 36 % of kidney and 19 % of liver transplant procedures are performed with organs obtained from LDs [4, 5]. In addition to liver and kidney transplants, living donation can also facilitate the transplantation of lung, intestine, uterus and pancreas segments [6–8]. Living donation rates vary from country to country. In Europe, living kidney donation is increasingly accepted, but there are considerable differences between countries in how often it is performed, the practices involved and the acceptance of donor–recipient relationships (see Table 13.1). Some countries, such as the Netherlands, Norway, Türkiye and the United Kingdom, have a long history of living donation with good results [4, 5].

Living kidney transplantation has been shown to be the best therapeutic alternative for patients with end-stage renal disease, because of several advantages compared with kidney transplant from deceased donors [9]:

a. Graft survival of LD kidneys is significantly longer.

b. The incidence of delayed graft function is lower.

c. Living donation allows for timely transplantation, enabling a recipient to receive a kidney transplant prior to dialysis. This is especially important for children. Besides improved patient survival, pre-emptive kidney transplantation has medical, logistical and economic benefits.

d. Living donation makes pre-treatment of the

recipient possible (e.g. in HLA-sensitised or ABO-incompatible patients).

In liver transplants, living donation offers its own set of advantages and challenges:

a. In Japan, South Korea, Türkiye and the USA, it is an important way to decrease waiting-list mortality by offering immediate transplants to patients at high risk of early mortality. There is clear benefit when the indications for transplantation are emergent – such as for acute liver failure, for acute on chronic liver failure or after primary non-function.

b. It is also significantly easier to find size-matched grafts for paediatric recipients using an LD than waiting for a matched paediatric/split graft.

c. With left lateral grafts being increasingly recovered using a laparoscopic approach, living donations are likely to increase even in countries with a developed deceased donation programme.

It is vital that Health Authorities and professionals who are responsible for transplant programmes promote deceased donation up to its maximum therapeutic potential. However, considering the large deficit of kidneys for transplantation compared to demand, at present and in the foreseeable future, member states should develop and optimise programmes for kidney donation from LDs based on recognised ethical and professional standards as a way to achieve self-sufficiency in transplantation. Liver donation from LDs should be considered in the context of lack of alternative transplant options in the necessary timescale.

13.2. Ethical and legal aspects of living donation

The safety and protection of the LD is essential for any programme and must be grounded on an appropriate regulatory framework, ethical principles and evidence-based clinical pathways. Living donation must be performed according to best practice and published evidence, following international recommendations from scientific bodies and societies such as the Amsterdam Forum on the care of the live kidney donor [10], the Vancouver Forum on the care of the live organ donor: lung, liver, pancreas, and intestine [11] and the KDIGO Clinical Practice Guidelines on the evaluation and care of living kidney donors [12].

Living donation must only be performed in centres authorised by the corresponding Health Authority and following strict ethical standards and regulations to minimise the medical and psychosocial impact of donation and to avoid organ trafficking and human trade, as recognised by the World Health Organization *Guiding principles on human cell, tissue and organ transplantation* [13] and the Declaration of Istanbul on Organ Trafficking and Transplant Tourism [14]. The Council of Europe Convention against Trafficking in Human Organs [15] and the Council of Europe Convention on Action against Trafficking in Human Beings [16] need also to be taken into account. The last two legal instruments criminalise the violation of basic principles in living donation, in particular the recovery of organs without valid consent or in exchange for financial gain or comparable advantage. Other standards that complete the international ethical and legal framework for living donation are the Council of Europe Convention on Human Rights and Biomedicine [17] and its Additional Protocol on Transplantation [18], as well as Directive 2010/53/EU of the European Parliament and of the Council on standards of quality and safety of human organs intended for transplantation [19].

Living donation is only acceptable when the following safeguards are ensured: the donor provides informed consent; selection criteria for donors are scrupulously applied and monitored; professional care is ensured; and medical and psychosocial lifelong follow-up is guaranteed. LDs must be informed about the potential medical and psychological risks of donation in the short and long term. It is important to ensure that this information has been understood by the donor before proceeding with the evaluation process. Furthermore, the economic, occupational and social consequences of donation must be conveyed in a complete and understandable fashion.

The donor must be considered competent to receive and weigh the information, must act willingly and must be free of any undue influence or coercion. All LD cases and the outcome of all LD nephrectomies must be registered for the purposes of traceability, safety and transparency of the activity.

Several European Union-funded projects (Accord, Elipsy, Eulid, Eulod, Odequs) have been set up to establish consensus and ascertain high-quality practices in all aspects of LD transplantation, including the establishment of national and international registries (see Figure 13.1) [19].

Reflection on the four principles – of beneficence (doing good), non-maleficence (avoiding harm), respect for autonomy and respect for justice (promoting fairness) – is essential in placing altruism as

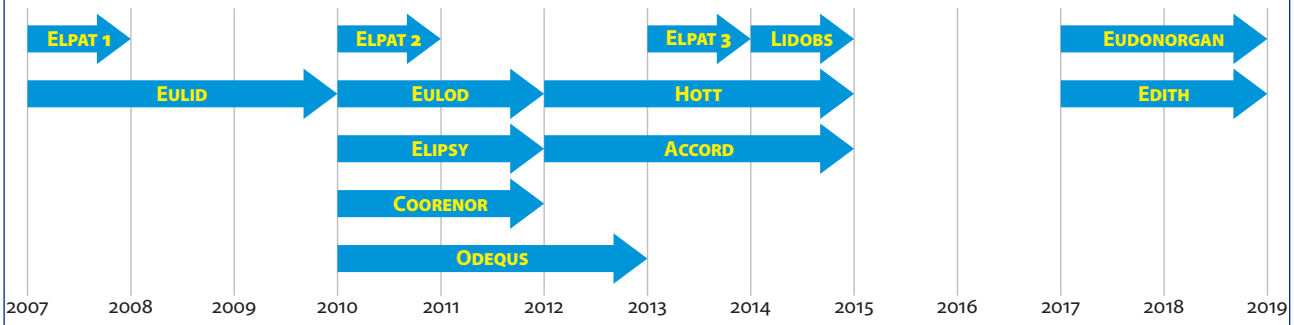
the fundamental ethical principle of living organ donation [20].

Donor consent is necessary, but alone it is not sufficient, to proceed with donor nephrectomy. Donor autonomy can never overrule medical judgment and decision-making. However, in selected cases, one could consider offering a second opinion. To ensure donor autonomy, it is important to

a. provide extensive specific information,
b. allow a reflection period,
c. exclude minors and persons unable to make decisions from being LDs [21].

It is good practice to involve an independent LD advocate or an independent assessor [22]. An LD advocate is defined as an independent medical, psychosocial and legal counsellor, with neither time constraints nor interests shared with any other party, someone who ensures the protection and safety of the LD [23]. Informed consent for donation should

Figure 13.1. **Summary of European Union-funded projects in living donation**



EULID (2007-2010)

Analysed the current European situation in legal, ethical, protection and registration practices related to living organ donation, in order to set standards and recommendations that guarantee the living donor's health and safety.

ELPAT Congresses (2007, 2010 and 2013)

ELPAT Congresses have brought continuity and progress in European research and dialogue on ethical, legal and psychosocial aspects of organ transplantation of the European Society for Organ Transplantation (ESOT). They aimed to integrate and structure this field of science by bringing together European professionals from different disciplines.

EULOD (2010-2012)

This project aimed to establish an inventory of living donation practices in Europe, to explore and promote living donation as a way of increasing organ availability, and to produce recommendations that improve the quality and safety of living organ donations in Europe.

ELIPSY (2010-2012)

The aim of ELIPSY was to guarantee the good quality of organ living donation for transplant through a living donor long-term psychosocial and quality of life follow-up. The recipient's outcome was correlated with these aspects and a follow-up methodology was created.

COORENOR (2010-2012)

The idea behind COORENOR was to establish a co-ordinated network of national programmes in the participating European member states in organ transplantation. It co-ordinated efforts of countries in eastern and western Europe, all having different approaches and programmes, to tackle the issues of organ procurement and transplantation.

ODEQUS (2010-2013)

ODEQUS' specific objectives were to identify quality criteria (QC) and to develop quality indicators (QI) at hospital level, in three types of organ donation: after brain death (DBD), after circulatory death (DCD) and living donation. Those tools are useful in self-assessment and external evaluation of hospitals, and in developing a European auditing model.

LIDOBS Conference (2014)

This event developed the exchange of experience and knowledge of Living Donation programmes in order to assure safety, quality and transparency of the procedures and high quality standards. The conference planned and set up a community of experts in Living Donation programmes named LIDOBS that continues to expand and increase the knowledge of donation and transplantation procedures.

HOTT project (2012-2015)

Combating trafficking in persons for the purpose of organ removal, this international research project aims to increase knowledge and spread information to raise awareness about the crime and improve non-legislative responses to it.

ACCORD (2012- 2015)

ACCORD was set up to improve the potential of member states in the field of organ donation and transplantation and to contribute to the effective implementation of EU Directive 2010/53/EU and the EU Action Plan on Organ Donation and Transplantation (2009-2015). The work on living donation has helped by creating a common methodology for registers of living donors.

EUDONORGAN (2017-2019)

This project has actively contributed to the increase in organ donation rates through the training of healthcare professionals and through social awareness events. The key objective is that the participants become advocates for organ donation.

EDITH (2017-2019)

The EDITH project aims to realise a European Living Donor Registry, supporting lifelong data collection. The intended result is a database, a web-based application supporting direct data entry and file upload, a data download facility, and a report facility complying with all legal requirements.

Source: Adapted from LIDOBS Conference recommendations [20] Final leaflet.

be obtained from the donor candidate in the absence of the intended recipient, family members and other persons who could influence the donation decision. Importantly, personal and medical donor information is confidential also in relation to the recipient. It is also important, however, that the intended recipient is aware of the risks to the donor. In addition, a donor candidate's decision to withdraw at any stage of the evaluation process should be respected and supported. Donor assistance could be needed in communicating a decision to withdraw to the intended recipient.

Reflecting this type of concern on how to protect donors, the LD Community of Practice of the American Society of Transplantation has recently published a guidance document [23]. To ensure application of the above-mentioned principles, regulations must include:

a. specific prohibition of donation by minors and persons unable to provide valid consent,
b. prohibition and criminalisation of trafficking in persons for the purpose of the removal of organs and organ trafficking,
c. authorisation of centres for recovering organs from LDs under the control of Health Authorities,
d. specific provisions to protect the non-resident LD, which should be linked to a policy of close co-operation between Health Authorities of different countries to implement a programme of referral and post-donation follow-up of non-resident LDs,
e. supervision of the LD process – evaluation, information and approval – according to national regulations, by an independent committee that includes healthcare professionals who are not involved in the organ removal or subsequent transplantation procedure (a specific ethics committee),
f. implementation of a reimbursement model of expenses related to donation to offset any negative economic consequences for donors and their families.

13.2.1. Consent and authorisation for living donation

Every aspect of donation from the LD – including consent, authorisation, procurement, follow-up, transparency, quality and safety systems, and the accreditation of transplant units and medical staff qualifications – must be governed by national regulations (see Chapter 17). This section (§13.2) gives especial emphasis to issues related to the valid consent of the LD and authorisation of the LD procedure.

Transplant centres differ in how donors are approached. The most common approach is that potential donors themselves contact the centre, after obtaining this information from the intended recipient. This also serves as an initial screening test, as only those donors who are sufficiently motivated would contact the transplant team. In addition, information to the general public on the possibilities and importance of living donation should be considered. To avoid conflicts of interest, it is good practice that potential donors are evaluated by someone other than the physician responsible for the recipient. However, in many hospitals this may not always be feasible.

Table 13.1. **Categories of living donation, based on the donor–recipient relationship**

Category	Sub-category	Definition
A – Related	The donor is genetically and/or emotionally related to the recipient	
	A1: genetically related	A genetic relation exists between donor and recipient (e.g. brother/sister, parent/offspring). Therefore a certain immunological compatibility exists too.
	A2: emotionally related	The donor is a genetically unrelated family member (e.g. spouse) of the recipient or a friend (to be considered as a family member).
B – Unrelated	The donor has no genetic or emotional relationship with the recipient. The relation between donor and recipient must be outlined further by a sub-specification. Immunological compatibility exists only by chance.	
	B1: paired exchange or crossover	By a controlled programme, unrelated donor and recipient pairs exchange grafts beyond any emotional or genetic relation, with the aim of overcoming immunological restrictions.
	B2: non-directed altruistic or anonymous	By a controlled programme, the donor can provide a graft to society which allocates this to a previously unknown recipient by defined rules.
	B3: directed altruistic	By a controlled programme, the donor provides a graft to a recipient of the donor's choice.

Source: WHO Global glossary of terms and definitions on donation and transplantation (adapted) at www.who.int/transplantation/activities/GlobalGlossaryonDonationTransplantation.pdf?ua=1.

Although most living donations (especially of kidneys) are made to a relative, centres follow different practices depending upon the type of relationship between donor and recipient (Table 13.1). The practice of non-directed and directed altruistic organ donation has emerged during the last two decades. There is no uniform practice in Europe. However, the number of transplants from such donors is increasing. Non-directed altruistic donors are controversial in some countries, while an important source of organs in other countries. In Europe it is currently most established in the UK and the Netherlands [24]. In addition to the 'routine' donor evaluation, there is usually a more thorough psychological assessment [25, 26]. The practice of directed altruistic donors is less frequent. The British Transplantation Society has developed guidelines for the evaluation of prospective directed altruistic donors, recommending an enhanced assessment by an independent assessor [27, 28].

In order to ensure that the donor has given valid consent, the following requirements must be respected:

a. At the start of the evaluation process, the potential LD must receive information on potential medical and surgical risks, both short-term and long-term. Both oral and written information (in the donor's native language) should be provided. After the initial information has been provided, the donor should be given time to think about the decision, before proceeding with the evaluation. Healthcare personnel should verify and document evidence that information has been understood.

b. The surgical procedure and its risks should be explained by an experienced surgeon. Information must include potential complications in the short and long term, both medical and psychosocial, including individual risks for the donor. Informing the donor about potential risks and obtaining informed consent are described further in Chapter 19.

c. Potential long-term risks should be explained by a transplant physician with experience and training in the communication of risks to potential donors.

d. The decision to donate must be voluntary and expressed without any pressure.

e. The LD must not demand or receive any material or financial benefits from the organ recipient, or from a third party, that could be considered as either coercion or reward.

f. The donor must be informed about the opportunity to revoke consent at any time during the evaluation process until the time of surgery, with no need for a specific formal procedure.

g. The potential LD must also be informed about possible adverse outcomes in the organ recipient: risk of organ rejection, medical and surgical complications and the possibility of organ failure.

h. Written informed consent must be given by the donor before finally being accepted as a living donor.

i. In some countries, after the potential LD has given consent, approval is required by an Ethics Committee. Such committees have to be independent from the procurement and transplant teams. In some countries the participation of the Ethics Committee is only mandatory in cases of unrelated donation. Some countries also require the approval to be confirmed by a court.

13.2.2. Authorisation for the living donation procedure

Beyond consent of the donor, some other aspects need to be considered before any living donation procedure is authorised:

a. Organ donation must be preceded by the necessary medical tests [29] (see tables 13.2 and 13.3), to be assured that the risk to the donor is acceptable.

b. The result of the medical assessment of the health status of the potential donor should be documented by a physician experienced and qualified in organ donation. The written statement must conclude that: 'there are no contraindications to organ donation'. This should include appropriate documentation.

c. The decision to accept a potential LD should be made by a multidisciplinary team.

d. If the risk to the donor is unacceptable, if there is doubt about the donor's ability to give informed consent, or if there are suspicions of coercion, organ donation must not proceed. This is regardless of whether the potential donor would consent.

e. In some countries, the potential organ recipient remains on the waiting list until the date of transplantation; up to that moment, the recipient is able to receive an organ from a deceased donor. In other countries, the patient is temporarily withdrawn from the waiting list once the evaluation of a potential LD has been completed and the transplant is likely to go ahead.

f. Each LD must be provided with permanent lifelong follow-up care related to donation.

This should be free of charge. If the donor declines follow-up, donation must be considered carefully in the context of the individual donor.

g. Information regarding health status at the time of donation, and during follow-up, should be documented in dedicated registries.

h. Living donation should be cost-neutral for the donor, who should receive reimbursement of all expenses related to donation and the recovery period. The unit performing the donation should ensure that the LD has proper insurance coverage (personally or from the recipient's insurance) to cover possible complications.

i. The act of living donation should not be a detriment to the patient securing employment or insurance coverage or obtaining credit, loans or mortgages.

j. Organ procurement from LDs must be performed only at authorised centres and by medical staff with formal permission and appropriate qualifications.

13.2.3. Authorisation of living donation from non-residents

Authorisation for donation in case of non-resident LDs must be undertaken according to the current legislation of the country where donation takes place. This type of donation cannot proceed unless full adherence to all recommendations specified in sections 13.1 and 13.2 is assured. Non-resident LDs are especially vulnerable. The donor–recipient relationship and the donor's motivations may be difficult to assess due to language barriers and cultural differences. Medical data may be incomplete. Therefore such transplant procedures should preferably be limited to first- or second-degree genetic relatives or spouses.

When performing an evaluation of a potential non-resident LD, one must be aware of the risk for organ trafficking, which may occur in many forms. In the appendix of Resolution CM/Res (2017) 1 from the Council of Europe, adopted on 14 June 2017 [30], there are recommendations on the evaluation, work-up, consent and follow-up of a potential non-resident LD. Especially, it states that 'Procedures should be in place to verify the claimed relationship between the potential donor and the recipient, and, where it cannot be proven, the donation should not proceed.' Furthermore, it states that 'Countries should ensure that LD programmes include procedures for LD assessment or advocacy, independent of the transplant team. This is particularly important for the non-resident donor' – to confirm that there is an informed consent without coercion. At especially high risk for organ trafficking is a donation from a directed altruistic non-resident donor [28].

The procurement centre must inform the potential donor of the necessity of lifelong and regular follow-up. Moreover, the procurement centre must ensure that the donor has the necessary means for follow-up either in their country of residence or elsewhere. As stated in the 2016 CD-P-TO Position Paper on the long-term outcome of living kidney donation, if there are no adequate lifelong follow-up arrangements, the donor should not be accepted [31]. Information about health status at the time of donation, and in the long term after procurement, must be documented in a registry in the procurement country.

Finally, Resolution CM/Res(2017)1 also states that when there is suspicion of organ trafficking, 'national protocols should specify the actions to be taken'. Although the actions taken may differ between countries, the resolution states further that these actions could include 'reporting the case to the national regulator and/or the law enforcement authority', and mentions the possible benefits of international data sharing.

13.3. Medical and surgical aspects of living kidney donation

13.3.1. Risks of living kidney donation

The risks of donor nephrectomy can relate directly to the nephrectomy itself or can arise in the mid- to long term.

Perioperative mortality, based on large series of mostly open nephrectomies, has typically been reported at 0.03-0.05 % [9, 32]. The immediate perioperative risks include: bleeding, deep vein thrombosis, pulmonary embolism, wound complications, urinary tract infection, pneumonia, atelectasis, intestinal complications, pneumothorax and a need for further surgery.

Minimally invasive LD nephrectomies – either laparoscopic or retroperitoneoscopic – have, in recent years, been shown to be superior to the open procedure regarding post-operative pain and hospital stay. Complication rates have been shown to be equal to the open procedure, although there may be a learning curve [33]. It would be desirable that transplant surgeons had expertise in at least two minimally invasive techniques in order to tailor the preferred surgical approach.

Previous studies have compared the long-term outcomes of kidney donors with the general population. This is an inappropriate comparison since kidney donors are healthy at the time of donation,

and the general population includes individuals with pre-existing diseases. During the last two decades, publications have emerged describing adverse outcomes after kidney donation. Several studies have found that kidney donation is associated with increased incidence of hypertension as well as proteinuria [30-31, 34-37]. The prevalence of hypertension in previous donors increases slowly. A study from the US found a prevalence of approximately 1% per year since donation [38]. A study from the UK found increased left ventricular mass one year after donation [39]. Females who have donated a kidney are at increased risk of pre-eclampsia in subsequent pregnancies [40]. Most disturbingly, a study from Norway with a median follow-up of 15 years found increased cardiovascular and all-cause mortality, evident at one decade after donation [41]. Although two other studies have not corroborated this finding, these had a shorter follow-up of around six years. Several studies have found an increase in end-stage renal disease after donation [2, 3, 42-45].

It is important that every donor can give valid consent for donation, after being appropriately informed of the risks [42]. Young donors and those from different ethnic backgrounds must be considered carefully in the context of their individual lifetime risk of donation and they should be appropriately counselled, using the best evidence that is available. Potential young donors of African-American ethnicity are at higher risk, with a higher lifetime incidence of hypertension, diabetes, renal disease and cardiovascular disease.

It is advisable to minimise risk factors and optimise the physical and psychological status of the donor before surgery, including physical activity, nutritional care and psychological support. After donation, the donor must be advised to maintain a healthy lifestyle, control body weight, promote physical activities and follow the recommendations on preventive control according to age and gender.

It is relatively common that potential living kidney donors are accepted although they have minor co-morbidities such as hypertension, impaired glucose tolerance or borderline renal function. Most transplant programmes have existing guidelines detailing how to handle such minor medical abnormalities [26, 46]. However, it is quite common that transplant centres have to make individual considerations of different co-morbidities in donors and make decisions based on clinical experience more than on evidence from the literature. Some aspects should be considered when evaluating donors with co-morbidities that are not absolute contraindications for donation. Firstly, consider whether donating a kidney could worsen the pre-existing condition. Secondly, one should consider whether the pre-existing condition could worsen the renal function in the remaining kidney.

However, the most important factor when evaluating such donors is age at donation. Since kidney donors are evaluated, and therefore considered healthy at the time of donation, most long-term risks will become evident only after a longer period of observation time. From the existing literature, it seems that both hypertension and end-stage renal disease develop only after a long period of observation time [2, 3, 37, 38]. The donor evaluation selects well in older donors, meaning that only the healthiest will be considered eligible donors. It selects less well in younger donors, since a large proportion of young donors will be considered eligible. Most importantly, young donors have a longer remaining lifespan with one kidney. Based on this, it is likely that a 20-year-old kidney donor with 60 years to live with one kidney faces a higher long-term risk after kidney donation than a 60-year-old donor who has 20 years left to live after donation. Hypertension is quite common in 60-year-olds. Consequently, if a transplant centre chooses to accept the healthy 20-year-old donor, it would be irrational not to accept a 60-year-old donor with well-treated hypertension [42, 47, 48].

13.3.2. Medical evaluation and exclusion criteria for living kidney donation

The aim of the donor evaluation is to ensure that the potential donor is in good health and has no unacceptable risk (bearing in mind the standard and accepted risks after donation), and that they are not under coercion, thus taking a free and informed decision.

We recommend that the physician responsible for the donor evaluation is not involved in the care of the recipient, since this may cause a conflict of interests. A complete past medical history and physical examination, as well as laboratory and imaging tests, should be performed according to established national and international guidelines. An example is provided in Table 13.2.

Medical criteria that could be considered as contraindications for living kidney donation are listed here:

a. Significant chronic disease (cardiovascular, pulmonary, hepatic, neurological or autoimmune). In cases of doubt, decisions should be taken on a case-by-case basis after discussion with relevant specialists.

Table 13.2. **Basic routine screening of the potential living kidney donor**

Assessment of renal function and urinalysis	**Cardio-respiratory system**
• Measurement of GFR • Dipstick for protein, blood and glucose • Microscopy, culture and sensitivity • Measurement of protein excretion rate	Chest X-ray Electrocardiogram Stress test Echocardiography
Immunological screening	**Virology and infection screening***
• Blood group • HLA-typing • Crossmatch	*Brucella* (where indicated) *Cytomegalovirus* Epstein–Barr virus Hepatitis B and C virus Hepatitis E virus (where indicated) HHV-8 and HSV (where indicated) HIV and HTLV 1/2 *Mycobacterium tuberculosis* (where indicated) *Plasmodium* (where indicated) *Schistosoma* (where indicated) *Strongyloides* (where indicated) *Treponema pallidum* *Toxoplasma* *Trypanosoma cruzi* (where indicated) Typhoid (where indicated)
Assessment of renal anatomy	**Blood tests**
Appropriate imaging investigations should allow confirmation of the presence of two kidneys of normal size and enable detection of any abnormalities of the collecting system and calcification or stone disease in the renal tract. They must also delineate the anatomy of the renal vasculature.	Haematological profile Complete blood count Haemoglobinopathy (where indicated) Coagulation screening (PT and APTT) G6PD deficiency (where indicated) Biochemical profile Creatinine, urea and electrolytes Liver tests Urate Fasting plasma glucose Glucose tolerance test (if fasting plasma glucose is 6-7 mmol/L) Bone profile Blood lipids Thyroid function tests (if indicated) Pregnancy test (if indicated) PSA (if indicated)

APTT: activated partial thromboplastin time; G6PD: glucose-6-phosphate dehydrogenase; GFR: glomerular filtration rate; HHV: human herpes virus; HIV: human immunodeficiency virus; HSV: herpes simplex virus; HTLV: human T-lymphotropic virus; PSA: prostate-specific antigen; PT: prothrombin time.

* For further details, refer to §13.6.1 and §8.4.1.

b. Obesity, even though it is modifiable. Body mass index (BMI) should be calculated. The decision to approve donor candidates with obesity and BMI > 30 kg/m² should be individualised in relation to the transplant programme's acceptable risk threshold [12].

c. Hypertension is considered a contraindication. Uncomplicated hypertension treated with one drug may be allowed in older donors.

d. Diabetes is considered a contraindication. Impaired glucose tolerance may be accepted in older donors.

e. Disorders requiring anticoagulation, depending on the underlying disease.

f. Chronic viral infection (HIV, HBV, HCV, HTLV) as outlined in section 13.6.1.

g. Active cancer or history of cancer. Donors with a history of cancer who have completed treatment and low risk of metastases and/or recurrence can be accepted under certain conditions, e.g. non-melanoma skin cancer, as outlined in section 13.6.2.

h. Proteinuria (e.g. > 300 mg/day). Microalbuminuria could be accepted in older donors.

i. Haematuria – potential donors with haematuria can be accepted in the absence of relevant urological or kidney disease. This requires additional investigations in the form of cystoscopy, imaging and a kidney biopsy.

j. Large differences between right and left kidney in estimated renal function. The kidney with the larger functional capacity should always be left in the donor. It is good practice to undertake a split function to determine the individual kidney function.

k. Nephrocalcinosis, bilateral kidney stones or recurrent nephrolithiasis. Single case of unilateral stone disease in the past history could be considered for donation after additional testing and evaluation. Preferably, the affected kidney is removed for transplantation and in some cases renal stones can be managed during back-table preparation immediately before implantation.

l. Low glomerular filtration rate (GFR) in relation to age.

13.3.3. Evaluation of donor GFR

Evaluation of the kidney donor candidate's GFR is a cornerstone of LD evaluation. Direct measurement of GFR based on the clearance of exogenous markers is the gold standard for evaluating renal function and it should be preferred in the context of LD evaluation. GFR estimating equations based on

serum creatinine suffer from a lack of accuracy for the evaluation of predonation GFR [49].

Regarding the threshold for allowing donation, the KDIGO guidelines recommend fixed, absolute thresholds of GFR beyond which donation is (> 90 mL/min/1.73 m^2) or is not (< 60 mL/min/1.73 m^2) indicated [46]. Furthermore, they recommend for donors with GFR 60-90 mL/min/1.73 m^2 that the centre makes a decision based on the centre's own 'risk threshold', using a web-based calculator [50] to estimate the lifetime risk of end-stage renal disease (ESRD) without donation, and to allow donation if this risk is sufficiently low in relation to the centre's own risk threshold [51]. This web-based calculator has been criticised by several authors [43, 44, 52] for having been constructed from population data with less than a decade of follow-up, and consequently not being able to assess the risk of ESRD from late events such as diabetes and hypertension. Based on these concerns, we do not recommend the routine use of this web-based calculator. On the other hand, many have advocated the use of age-adapted values to define GFR adequacy for donation [26, 53, 54]. This latest approach may seem physiologically plausible given, on the one hand, the well-recognised relationship between age and GFR [55], and the uncertainty surrounding the actual pathogenicity of age-related GFR decline [56].

In conclusion, since there is a natural decline in GFR as part of ageing, the acceptance limit for GFR could be lower in older individuals, and higher in younger individuals. The guidelines from the British Transplantation Society have put this into practice [26].

13.4. Medical and surgical aspects of living liver donation

13.4.1. Risks of living liver donation

Most LD liver donations are still carried out by open surgery, though there is an increasing body of evidence supporting the minimally invasive approach to LD hepatectomy, without compromising LD safety.

The short-term safety issue is different from the issue in LD nephrectomy, because the peri-operative risk is higher, particularly in adult-to-adult LD liver transplantation. Taking into account the increased mortality risk compared with LD nephrectomy, the pre-operative assessment of donor risk and motivations is important. Also to be considered are: the level of surgical LD liver resection and hepato-biliary surgery competence, recipient status and alternative deceased donor organ availability. Even in transplant centres with substantial LD liver resection competence, the indication should be carefully considered.

The peri-operative mortality rate has been estimated at 0.1-0.4 %, and the surgical complication/morbidity rate has been reported to be 5-40 %, with the majority of complications lying in the spectrum of Clavien–Dindo Grade I or II [57-59]. Right-sided resections have been considered to involve a higher risk. The mortality rates after donor right hepatectomy surgeries (liver graft including segments V, VI, VII and VIII) performed from 1990 to 2000 were reported as around 2 %. Through the years this rate has declined to 0.4-0.5 % [60]. In an international survey including 21 countries where LD liver transplantation (LDLT) was performed, the morbidity and mortality rates for 11 553 liver donors in 148 centres were 24 % and 0.2 %, respectively. In a recent systematic review of 63 published articles regarding morbidity and mortality for LDLT, it was shown that between 1999 and 2017 there were 23 reported cases of peri-operative donor deaths [61]. The primary cause of death was post-operative sepsis, accounting for 30 % of cases. In another registry analysis, which included 4 598 LDLT performed in the United States and Europe, seven donor deaths were reported that had definite relation to donor surgery, representing a 0.15 % donor mortality rate [62]. In a study from the US, long-term mortality was not found to be higher than that in healthy controls [63].

Donor morbidity rates vary considerably among studies and have been reported to range anywhere from 9 % to 78 % [61]. The most common complications are related to the biliary system. Biliary fistulae can lead to collections developing adjacent to the transection surface, which usually resolve with conservative management but occasionally require percutaneous drainage. Stenosis of the remnant biliary system in the donor is less common, with an incidence of around 1 % [64]. The incidence of complications after liver donation is difficult to assess due to the lack of uniformity of the available data. Although there is considerable variation in the overall complication rates published from single centres, most cumulative series demonstrate low overall morbidity rates for LDs. The most common medical complications after donation are fever, pneumonia and urinary tract infection. Complications related to surgery include bleeding, wound infections, incisional hernias, portal vein thrombosis/strictures and biliary leaks/strictures. Biliary leaks can cause collections adjacent to the resection line, usually resolving with conservative treatment, but sometimes requiring percutaneous drainage or endoscopic retrograde cholangio-pancreatography (ERCP). Ste-

nosis of the biliary system is less common, around 1 %. When analysing complications according to the type of hepatectomy performed, right-lobe liver donation was associated with a higher rate (range 20-60 %, overall approximately 35 %) and with more severe complications than left-lobe liver donation [59, 60].

13.4.2. Medical evaluation and exclusion criteria for living liver donation

LD liver transplantation is an important strategy to consider in many patients waiting for transplant and has been shown to achieve excellent outcomes in the recipient. It is based on the principle of double equipoise, where donor risk is justified by recipient benefit. However, donor safety and not recipient benefit should remain the primary concern for the transplant team. The optimisation of donor-selection criteria, the experience of the surgical team in hepatobiliary and transplant surgery and the establishment of careful post-operative management protocols are essential to achieve low donor morbidity rates.

A summary of the routine screening of potential living liver donors is provided in Table 13.3.

Once accepted for the liver transplant waiting list, patients can be offered the possibility of LD liver transplantation in centres where the procedure is performed. Evaluation of possible donors starts when they voluntarily request information about the process. In general, a maximum age of 55 and an apparently normal state of health is recommended to start the evaluation. Blood group compatibility between the donor and the recipient is no longer considered essential for performance of liver transplantation. The evolution of desensitisation protocols, especially the success of rituximab [65] in preventing antibody-mediated rejection, has led to marked improvements in graft and patient survival of patients undergoing ABO-incompatible liver (ABOi) transplants. According to recent literature, 1- and 5-year patient survival after ABOi LT was 91.8 % and 88.4 %, respectively, compared with ABO-identical survival rates of 91.5 % and 86.7 % respectively [66].

If the ethical and legal criteria are fulfilled, the evaluation process may begin. It involves hepatologists, surgeons and psychologists. An extensive evaluation of the health status of the potential donor is mandatory in order to minimise the impact of a major abdominal surgery procedure. It is very important to rule out the presence of liver, infectious or neoplastic diseases. Also, a psychological assessment must be performed.

Table 13.3. **Basic routine screening of the potential living liver donor**

Assessment of liver function	**Cardio-respiratory system**
AST, ALT, bilirubin, ALP, albumin, GGT PT, INR	Chest X-ray Electrocardiogram Stress test Echocardiography
Immunological screening	Virology and infection screening*
Blood group HLA-typing (optional) Cross-match	*Brucella* (where indicated) *Cytomegalovirus* Epstein–Barr virus Hepatitis B and C virus Hepatitis E virus (where indicated) HHV-8 and HSV (where indicated) HIV and HTLV 1/2 *Mycobacterium tuberculosis* (where indicated) *Plasmodium* (where indicated) *Schistosoma* (where indicated) *Strongyloides* (where indicated) *Treponema pallidum* *Toxoplasma* *Trypanosoma cruzi* (where indicated) Typhoid (where indicated)
Assessment of liver anatomy	**Blood tests**
Appropriate imaging investigations should allow confirmation of the liver size and uncover abnormalities of the biliary ducts, fatty liver disease or cirrhosis/fibrosis. They must also delineate the anatomy of the liver vasculature. Liver ultrasound with Doppler Fibroscan (optional) Thin-slice triphasic CT scan MRI cholangiography	Haematological profile Complete blood count Haemoglobinopathy (where indicated) Biochemical profile Creatinine, urea and electrolytes Proteinogram Blood lipids Thyroid function tests Alpha-fetoprotein B-HCG NSE CEA Pregnancy test (if indicated) PSA (if indicated)

APTT: activated partial thromboplastin time; B-HCG: beta human chorionic gonadotropin; CEA: carcinoembryonic antigen; GGT: gamma-glutamyl transferase; HHV: human herpes virus; HIV: human immunodeficiency virus; HSV: herpes simplex virus; HTLV: human T-Lymphotropic virus; NSE: neuron-specific enolase; PSA: prostate-specific antigen; PT: prothrombin time.

* For further details of virology and infection screening, refer to §13.6.1.

The evaluation of the liver itself in an LD has two aspects:

a. to ensure that a graft of adequate size is procured,

b. to ensure that the remaining liver in the donor is not compromised and is able to sustain adequate liver function.

In this regard, a precise analysis of the liver volume and its detailed vascular and biliary anatomy is essential to determine donor suitability. This knowledge, before obtaining the graft, is very important for guaranteeing the success and safety of the surgery, in both the donor and the recipient.

A detailed radiological assessment is a prerequisite for a successful donor operation. A volumetric assessment of the total liver volume of the donor liver, the expected graft weight for the recipient, and the residual amount of hepatic parenchyma are all calculated. While a small graft with a graft–recipient body weight ratio < 0.8 may lead to the feared small-for-size syndrome, it is even more important to make sure that there is sufficient liver parenchyma – enough future remnant liver volume – remaining to avoid liver insufficiency in the donor after surgery.

The second aspect of the radiological assessment deals with a thorough evaluation of the biliovascular anatomy. With growing experience, the absolute anatomic contraindications to donation have shrunk significantly. Nevertheless, identification of these contraindications and surgical preparation for the anatomical difficulties expected are paramount in maintaining the high safety standards required for a successful LD liver transplantation programme. The hepatic artery, portal vein and pattern of hepatic venous drainage are all assessed for suitability for potential donation. Variations of hepatic venous drainage have to be assessed pre-operatively in order to formulate a surgical plan that prevents congestion of the anterior sector of the graft. MR cholangiography is the mainstay of evaluation of pre-operative biliary anatomy. The bile duct is the structure with the largest number of anatomical variations, although this is not usually a contraindication for donation.

It is also essential to evaluate for the presence and degree of liver steatosis. Non-invasive methods, such as utilisation of the liver attenuation index calculated using non-contrast CT images or fibroscan for measuring liver stiffness, provide a fairly accurate assessment of the degree of liver steatosis and fibrosis.

The selection of either right or left lobe hepatectomy/transplantation requires individualising each particular case and choosing the best procedure depending on the particular characteristics of the donor and the recipient.

13.5. LD lung, pancreas, small bowel and uterus transplantation

In order to increase the number of suitable lung donors, mainly for small and critically ill patients, the use of lobar lung LDs was introduced in the 1990s. LD lobar lung transplantation provides a similar survival rate to deceased donor lung transplantation, even for very ill patients. Surgical techniques typically include recipients' bilateral pneumonectomy and subsequent implantation of a right lower lobe from one donor and a left lower lobe from the second donor. Donor risks have been considered acceptable [67]. However, in a US report from 2014 [68], major complications occurred in 18 % of donors. In countries with deceased donation programmes, living lung donation is a rare procedure after implementation of lung allocation systems.

Live pancreas donation is another rare procedure. Surgical complications include spleen lacerations and pancreatic leakage. There are no survival data available. Lam *et al.* found increased risk of diabetes among donors, with 27 % of donors having been prescribed antidiabetic medication at a mean of 16 years after donation [69].

Small bowel donation is a rare procedure, performed only in a few centres worldwide [70].

Living uterus donation is a rare procedure. There have been few reports, mainly from Sweden, but also from India and from the US, with successful pregnancies post-transplant [71].

13.6. Medical evaluation of the LD with regard to the risk of disease transmission

Disease transmission from donor to recipient can occur in the context of living donation. Unlike the situation with deceased donors, in less urgent cases sufficient time for appropriate donor investigations and possible treatment in advance is available. Therefore more extensive diagnostic work-up for safer risk assessment should be implemented. In general, the investigations and procedures recommended in deceased donors should be performed in LDs (see chapters 6 to 10), but the risk–benefit assessment of a possible donor–recipient pair can be done without time constraints.

13.6.1. Risk of transmission of infectious diseases

Addressing the risk of transmission of infectious diseases through living donation adheres to the same principles that apply in deceased donation, as outlined in Chapter 8. In the case of an LD, an infection can be acquired between screening and organ recovery. Therefore, basic LD screening tests must be performed both at initial counselling and again at the final counselling and/or before the organ is procured. Results must be available before the organ is removed for transplantation. Counselling of the donor and recipient must include the information that infections may be acquired during the period from initial or final screening and counselling up to the day of transplantation. Therefore, transmission risks still exist despite appropriate screening, and such transmissions have indeed occurred.

Some special considerations might help in reducing the risks of transmission of infectious diseases through an LD:

a. LDs should be screened with serology for HIV, HBV, HCV and HEV shortly (one week) before organ donation in order to minimise risks due to undisclosed risk behaviours. NAT testing should be reserved to high-risk donors. HEV NAT testing should be performed only in areas with high prevalence of HEV infection or if the donor has undiagnosed elevation of liver function tests.

b. In the case of vaccinations with live vaccines, transmission of a vaccine-derived pathogen can be avoided by postponing the transplantation by 4 weeks if necessary (see §8.2.4). In LDs, it is advisable to perform HAV and HBV vaccinations before donation in non-immunised donors (see §8.6.2.10 and §8.6.2.11), and also to complete vaccinations as recommended by the local healthcare system.

c. In the case of Epstein–Barr virus D+/R–, there is a high risk of post-transplant lymphoproliferative disorders and ideally this should be avoided. In the case of Epstein–Barr virus D+/R– transplants, protocols for close monitoring of such recipients for post-transplant lymphoproliferative disorders could facilitate earlier diagnosis (see §8.6.2.7).

d. In the case of a kidney donor with HBV infection or HCV infection, the principles outlined in sections 8.6.2.11 and 8.6.2.12 should be applied. Living kidney donors with HCV infection and viraemia should receive treatment with the new direct-acting antiviral (DAA) drugs before donation. If they achieve sustained virological response, living donation and transplantation from such HCV-negative donors may be possible. It is unlikely that a living kidney donor with sustained virological response will transmit HCV through the graft, but this has not been confirmed yet. In any case, proper follow-up of the donor and recipient (HCV-RNA measurements) will help to identify the need for intervention. Beyond this level of follow-up, the pathways discussed for deceased donors might be applied in LDs based on case-by-case decisions (see §8.6.2.12).

e. Transmission of Kaposi sarcoma herpes virus (HHV-8) from organ donor to recipient has been documented through seroconversion and by molecular epidemiologic studies (see §8.6.2.8). Although the optimal serologic assay has not been determined, the combination of whole virion ELISA (enzyme-linked immunosorbent assay) and lytic immunofluorescence assay should be utilised to improve sensitivity and specificity. The screening of donors and recipients for HHV-8 in low-prevalence countries is currently not recommended. However, in high-prevalence countries, screening is advised, and donors with positive HHV-8 serology should be excluded from organ donation due to the increased risk for the recipient of developing HHV-8 associated diseases. Infected recipients may experience fever, splenomegaly, lymphoid hyperplasia, pancytopenia and occasionally rapid onset cutaneous or visceral Kaposi sarcoma. A very severe clinical picture and high mortality associated with primary HHV-8 infection has been observed in kidney and liver transplant recipients. Use of organs from HHV-8 positive donors in HHV-8 positive recipients might be allowed if the recipient is informed about the risk of developing HHV-8 related diseases post-transplant independently of the donor's HHV-8 positivity.

f. Seasonal screening for West Nile Virus (WNV) or other seasonal infectious diseases using NAT should be considered, at least in the case of local epidemics of WNV. For laboratory screening, LDs should be screened by WNV-NAT within 7-14 days before donation. The use of serologic testing offers an additional potential strategy to screen potential LDs for WNV, but it has significant limitations due to performance and interpretation. During the mosquito season, prospective LDs should be counselled to use personal protective measures against mosquito bites, such as using insect repellents and

avoiding outdoor activities between dusk and dawn. These practices are meant to mitigate the risk of acquiring WNV between diagnostic testing and organ donation.

g. Anti-HTLV-1/2 screening should be considered in donors coming from geographic regions with a high prevalence of HTLV-1/2 infections (see §8.6.2.16). D+/R– combinations are usually not accepted, though evidence-based policies do not exist.

h. As a minimum, acute or chronic persisting bacterial infections or colonisation of the organ to be transplanted should be treated in LDs. Those colonised or infected with multi-drug resistant bacteria should have documented eradication of the pathogen before organ donation. This does not apply to simple faecal carriage of multi-drug resistant pathogens.

i. Donors with curative treatment of tuberculosis can be accepted with some care and follow-up of the recipient. The risk of latent tuberculosis with transmission risks (as outlined in §8.4.6) should be considered; in living donation, interferon-gamma release assay (IGRA) tests of donor and recipient are helpful. LDs with a positive tuberculin skin test (TST) or IGRA should be offered treatment for latent tuberculosis prior to donation or as per local or national guidelines. Because completion of this treatment may delay the transplant and adversely impact the recipient, expert opinion is that each situation should be individualised, but treatment does not need not be completed before the transplant occurs. There are no data on the optimal duration of possible latent tuberculosis therapy in this setting. Information about tuberculosis status and treatment history should be noted in the medical record of the organ recipient. Chemoprophylaxis should be considered for recipients whose donor tuberculosis screening test (TST or IGRA) was positive, in cases where the donor did not receive either any or sufficient chemoprophylaxis. Recipient risk of isoniazid (INH) toxicity must be weighed against the risk of donor-derived tuberculosis transmission; drug interactions with transplant medications and rifamycins (rifampicin, rifampin, rifabutin, rifapentine) should also be carefully considered after transplant. Clinicians should consider the impact of local resistance rates when developing effective chemoprophylaxis protocols, and should refer to local or national guidelines.

j. Disseminated fungal infections (or fungaemia) must be eradicated completely before donation. For localised infections, case-by-case consideration is necessary (see §8.6).

k. Active parasitic disease of the donor is a contraindication for donation. Exceptions may be possible if unacceptable risks for the recipients have been ruled out by transplant infectious disease specialists (see §8.7).

l. *Trypanosoma cruzi*, the parasite responsible for Chagas disease or American trypanosomiasis, has a predilection for muscle, heart and neurological cells. Screening is important for residents of, immigrants from or travellers to endemic areas (Latin and South America, see §8.7.3).

m. Strongyloidiasis typically occurs only in the setting of specific environmental exposures; thus, screening all potential LDs is not indicated. Screening is justified for the following potential organ donors:

i. Persons who were born in or lived in tropical or subtropical countries where sanitation conditions are substandard. This includes candidates with prior military service in endemic areas. Strongyloidiasis has occurred in most countries, with the exception of Canada, Japan and northern Europe.

ii. Persons with unexplained oeosinophilia and a history of travel to an endemic area.

iii. Those born in the United States who have had significant exposure to soil in Appalachia or the south-eastern United States.

iv. Persons reporting a prior history of *Strongyloides* infection [72]. *Strongyloides* IgG antibody testing is readily available in many reference labs. Test sensitivities vary and false-negative results have occurred, including in early infection and immunocompromised hosts. Indirect immunofluorescence assays have improved sensitivity; however, they are generally only available through research laboratories. There is no standard commercially available confirmatory testing for antibody-positive specimens; false-positive tests are uncommon. Individuals with a history of treatment for *Strongyloides* infection may have persistent antibody response; consequently, those donors should undergo further evaluation by an expert in infectious diseases.

n. Risks of infections should also be considered according to lifestyle, living and sanitary conditions, vertical transmission, etc., as outlined

in section 8.10. Surveillance of disease transmission vectors contributes to detection of new transmission risks in LDs too.

o. Preventive strategies that can minimise the risk of donor-derived diseases among potential recipients are summarised in section 8.12.

p. Not enough data exist for patients under treatment for HIV infection in Europe for conclusions to be drawn and recommendations to be made about whether they can be considered as potential LDs. Transplantation to HIV-infected recipients is possible (see §8.6.2.15). There are reports that LDs with HIV have donated, but one must consider the risk of HIV-associated kidney disease in the donor, and future increased risk of ESRD after donation [73].

q. Migrants and people who regularly travel abroad could be at risk for certain geographically restricted infections, depending on the prevalence of the particular infection in their country of origin/travel, their vaccination status, the countries visited during their journey and the conditions experienced. Thus, when serving as organ donors, this should be considered before the transplant takes place, to reduce the risk of transmission of geographically restricted infections, although these may be rare in the country where the transplant is performed. Similarly, recipients may experience reactivation of the respective pathogens under immunosuppression. It is advisable to refer to the epidemiological data of health organisations on infectious diseases according to the country of origin/travel. Moreover, immunisation status should be evaluated and, if there is uncertainty, the potential donor/recipient should be considered as unvaccinated [13, 74, 75].

13.6.2. Risk of transmission of malignancies and other diseases

It is important to adhere to the principles applied to malignancies and other diseases in deceased donors, as outlined in chapters 9 and 10. Any active malignancy must be ruled out during the work-up of the LD. It is important to verify that the potential donor has participated in national screening programmes, and basic cancer screening tests should be implemented as part of donor evaluation. In the rare case of allowing donation from a donor with previous malignancies at low risk of transmission, the curative treatment and the length of disease-free period must be verified. However, exceptions are sometimes made on a case-by-case basis in patients with very low risk of transmission.

Regarding donor transmission risks for specific malignancies, see Chapter 9.

13.7. Psychosocial aspects of living donation

13.7.1. Potential effects on LDs

Living donation and transplantation has potential benefits also for the donor (e.g. increased self-esteem, improved quality of life, improved social and family situation). However, there are also potential psychological problems that might occur during or after living donation that need to be considered. In the 2013 RELIVE study, 9 % of LDs showed an impairment of their physical health-related quality of life and another 9 % of donors had significantly impaired mental health-related quality of life [76]. Deterioration of the donor–recipient relationship has been observed in up to 14 % of cases [77].

13.7.2. Psychological evaluation of LDs

Many transplant centres have some form of psychological evaluation carried out by a transplant co-ordinator, nurse, social worker, psychiatrist or psychologist. The pre-donation psychosocial assessment is intended to prevent donation from individuals with significant risk of developing mental health disorders, or to identify whether precautions should be taken. Therefore, it should be aimed at the assessment of competence; knowledge and understanding of donation risks and benefits; psychological functioning, motivations and expectations; the donor–recipient relationship; and social support (see Table 13.4) [78, 79].

Pre-donation psychological assessment should be performed through semi-structured interviews supported by reliable and valid psychometric tests adapted to the cultural characteristics of the donor. The interview should be performed by the professional who is responsible for ensuring that the donor is aware of the consequences of their decision (somatic, mental and psychological, as well as personal, familial and professional).

An interview with the LD is required in order to:

a. understand how the process of decision making has been performed;

b. evaluate family and social environment and social support;

c. review employment (contract type, labour implications of their decision), including the

economic impact of their decision and the measures adopted to counteract any adverse situation.

In particular, the family environment should be explored in order to detect any family conflicts, and to find out who will be in charge of post-donation care and how the welfare of the person(s) taking charge has been planned in the event of any complication.

It is important that the recipient not be present during the interview in order to ensure that the donor speaks freely, expressing the donor's own concerns and doubts.

It is also important to assess the donor's biological risk behaviours (e.g. sexual promiscuity, drug addiction, travelling to endemic areas of tropical diseases) and to ensure that the relevant serological tests have been performed and that these are negative.

There should also be an evaluation of how much the donor knows about the recipient's disease and other potential treatment. For many donors, part of making an informed decision is to know about the potential benefits and risks for the recipient. However, this discussion should not reveal details of the recipient's disease. This could be a difficult situation, since in some cases it would be important for the donor to know if there was a high risk of recurrence of the primary kidney disease. In other cases it would be important for the donor to know about the prognosis with further dialysis treatment or the consequences for the specific recipient if waiting for an organ from the deceased organ waiting list. There are several dilemmas in this situation, but it is important to help ensure that the donor has all the relevant information needed before making a decision whether to donate an organ or not.

Table 13.4. **Risks and exclusion criteria for living donation detectable during psychosocial evaluation**

A. Absolute contraindications	
Coercion	Besides cases of flagrant coercion, any pressures from family or from the donor–recipient relationship must not impose either an unacceptable medical, psychological or social risk to the donor, nor a shortening of the period between consent and surgery set aside for potential reconsideration of the decision to donate.
Financial gain or comparable advantage	
Active substance abuse or dependence without willingness to receive appropriate treatment	
Mental health disorder or psychological instability that compromises the ability to give free and informed consent. Mental health disorder or psychological instability that, according to the clinical judgment of the mental health specialist, may worsen as a consequence of the donation process. Mental health disorders requiring pharmacological treatment for stability incompatible during surgery or at post-donation.	
Cognitive disability preventing free and informed consent	Donors must demonstrate capacity to understand the information included in the informed consent at a level of complexity adapted to each donor.

B. Risk factors	
Extreme and maladaptive personality traits	For instance, conscientiousness and compulsiveness (lowest: poor adherence to healthcare recommendations; highest: rigidity towards receptors' health behaviours); impulsiveness; narcissism; histrionism; emotional dysregulation.
Understanding of donation risks and benefits, and ambivalence	Includes awareness of the possibility of renal failure in the future or being unable to donate to a spouse/partner/significant other. Donors with a strong feeling of making an autonomous decision cope better with the post-operative course. Ambivalence worsens physical and mental outcomes [80], whereas comfort with decision to donate protects the mental health quality of life [76].

Motivations	Verify the absence of potentially iatrogenic motivations or indicate a pre-donation intervention and close monitoring after donation (e.g. delusional or megalomaniac, placing receptor in debt to donor, compensating for past mistakes or restoring position in the family, donation as a moral obligation [81], desire for recognition, using donation for publicity).
Expectations	Detect and modify unrealistic or idealised expectations (e.g. improve relationship with recipient [68]; solve psychological problems and familial conflicts [82]; interpersonal benefit; and shorter time of recovery than can be expected [76]). Detect and modify expectations of low manageability of transplantation demands. Expectations define transplantation success from the patient's point of view [83].
Donor–recipient relationship	In 20 % of all cases, unresolved problems appear (e.g. unilaterally dependent relationships), and half of that 20 % resign from being a LD [82]. In general terms, donation amplifies the quality of the pre-existing relationship, both for better and for worse.
Limited family and social support, including health providers	Feeling ignored and perception of low attention after surgery worsens quality of life, whereas strong perceived support is protective [84]. Lack of a partner predicts worse mental health after donation, while generally lower social support contributes to the maintenance of pre-donation lower mental health.
Lack of disclosure to others potentially affected by living donation	Knowledge by family of possible donation is a protective factor for outcome. Family conflicts about other potential alternatives to donation (e.g. other donors available) may cause diminished support for donation.
Fear of kidney failure	Some 13 % of living kidney donors report moderate or high fear of renal-related health problems after donation [82, 85].
Stress management and current coping resources (optimism, coping strategies and resilience)	History of maladaptive emotional responses to, and management of, stressful life events. Higher optimism leads to expectations of benefit, whereas lower optimism is associated with expectation of negative consequences from donation [76]. An avoidant coping style predicts worse mental health after donation.

13.8. Living donation registries: regulatory audit

LD registries are needed for quality and safety control, for transparency of practice and to facilitate evaluation of the consequences of donating an organ. Systematic data collection makes it possible to obtain sufficient information to define and facilitate long-term follow-up, to document the outcomes and to investigate causal relationships between pre-donation risk factors and future prospects, including cardiovascular events, kidney/liver failure and death. Therefore, all Council of Europe member states must ensure that harmonised national LD registries are developed and maintained according to Resolution CM/Res(2015)11 [86]. The appendix to this resolution provides general guidelines for the construction of national/international LD registries, and the explanatory memorandum details the parameters (mandatory and optional) for data to be collected.

In the EU, Directive 2010/53/EU on standards of quality and safety of human organs intended for transplantation establishes the legal requirement for EU countries to develop a 'register or record of LDs' [19].

International professional standards, such as the 2004 International Forum on the Care of the Live Kidney Donor [10] and the KDIGO guidelines [12], have also recommended regular lifelong follow-up and monitoring of LDs, and the establishment of dedicated LD registries.

Health Authorities must conduct regular audits of, and checks on, centres authorised for LD evaluations and transplantation.

The Lidobs Conference (2014) first enabled an exchange of experiences and knowledge of living donation programmes in order to assure the safety, quality and transparency of the procedures and high-quality standards. The conference aimed to set up a community of experts in living donation programmes named Lidobs [87] that would continue to expand and increase knowledge of donation and transplant procedures through a network (http://lidobs.eulivingdonor.eu/). The Edith project (https:

//edith-project.eu) aimed at establishing a European LD Registry, building on recommendations from the ACCORD project.

13.9. ABO blood group and human leukocyte antigen incompatible transplantation

ABO-incompatible (ABOi) transplantation has been introduced during the past 30 years worldwide as a strategy to expand the donor pool in LD transplantation – mostly for kidneys. The success of centres performing ABOi transplantation is related to strict adherence to a protocol in an ongoing structured programme. Such protocols take into account all recipient- and donor-related obstacles associated with antibody-incompatible transplantation, including effective desensitisation protocols, subsequent adapted immunosuppression and knowledge of the immune pathogenesis. The key issues in ABOi transplantation are:

a. pre-transplant antibody removal by the use of either plasmapheresis or cascade filtration, and unselective or selective immunoadsorption to prevent hyperacute rejection,
b. intravenous immunoglobulin,
c. B-cell depletion by rituximab,
d. patient-tailored maintenance immunosuppression.

Individualised immunosuppression is combined with monitoring for early detection of re-increasing antibody titres, mainly during the first two weeks after transplantation. Thereafter, even when antibodies recur at high levels, they do not seem to harm the kidney transplant, a phenomenon that is called 'accommodation'.

For the most recent era, since 2000, overall patient and graft survival rates are comparable to that of ABO-compatible kidney transplantation. However, there is increased risk of infectious complications, probably due to increased immunosuppression [86, 88-91]. Because of this, some centres now recommend ABO-incompatible pairs to join kidney paired exchange programmes (KEP).

There is an increasing population of highly sensitised patients with donor-specific anti-HLA antibodies (DSA) against an available donor. Therefore several desensitisation protocols have been developed, which generally use plasma exchange with infusions of intravenous immunoglobulin and rituximab, aiming to eliminate or reduce anti-HLA antibody levels so that the cross-match becomes negative in order to enable transplantation. The recipients experience high rates of antibody-mediated rejection; and, the higher the pre-transplant DSA levels were, the more substantial is the increase in the rate of antibody-mediated rejection [92]. Long-term survival after transplantation across the HLA barrier is impaired [93, 94].

13.10. Kidney paired exchange programmes

The strategy of KEP or kidney-sharing schemes was first introduced 30 years ago. When multiple transplant centres within the same country combine their registries, they can achieve more matches. This has been accomplished in several European countries, as well as in Australia, Canada and the US. Besides the success of large multi-centre or national KEP registries, single-centre programmes also exist, which are logistically simpler but may lack the benefits of a larger pool size. However, given the facility of matching more pairs within large KEP programmes, co-operation between more countries is evolving [95]. There are large differences between the different national kidney exchange programmes in Europe [24].

Donor–recipient pairs are entering the exchange programmes mainly because of immunological incompatibility for HLA (e.g. positive cross-matches, and/or high titre donor-specific antibodies) and/or for ABO incompatibility. Furthermore, the use of kidney sharing schemes, while overcoming ABO-incompatibility, often facilitates transplantation in highly HLA-sensitised recipients. In such cases, KEP can involve a manageable ABOi pair, in order to avoid the HLA barrier. In addition, combining kidney exchange with various desensitisation strategies increases the possibilities of finding a compatible donor. Also pairs that are borderline-compatible could benefit from achieving a better HLA-match. Other donor–recipient incompatibilities that could be handled by kidney exchange are age and kidney size [96].

Finally, the use of altruistic donors to start linear or domino chains of transplantations, otherwise known as non-simultaneous (or simultaneous) extended altruistic donor chains, is another option for enhancing the success of KEP [97]. By donating to a KEP and starting a domino chain, the impact of an altruistic donation is multiplied. It has also been proposed to use deceased donor kidneys to help initiate a donor chain [98].

With regard to the results of kidney sharing schemes, the overall match rates are approximately 50-60 % in a large registry with more than 1 000 pairs.

However, those recipients that are highly sensitised (PRAs > 95 %) and/or are blood type O achieve match rates of only 15 % [96].

13.11. Conclusion

Transplantation of grafts procured from properly performed living donation procedures is complementary to grafts procured from deceased donors. Legal, ethical, psychosocial and medical requirements have to be considered, since healthy individuals are exposed to risks for the benefit of someone else. LD transplantation must be performed according to evidence, following international recommendations from scientific bodies and societies. Registries and follow-up of LDs are mandatory for the purpose of traceability, safety and transparency. In the treatment of small children with end-stage organ failure (specifically not included), the experts contributing to this chapter agree on considering living donation as the preferred option.

Research agenda

From the literature and discussion of the available evidence, several topics were identified for which evidence is inconsistent, insufficient or non-existent. For the benefit of patients undergoing transplant procedures, the authors of this guide recommend that future research, where possible in well-designed RCTs, should focus on these research gaps:

During the last decade, studies in kidney donors have shown increased blood pressure [34, 36, 37], increased risk of pre-eclampsia [40], increased left ventricular mass [39], increased proteinuria [35] and increased incidence of end-stage renal disease [2, 3, 50] among previous kidney donors, when compared to healthy controls. One study has shown increased long-term mortality [3], a finding that needs corroboration in future studies.

There have been fewer studies performed in living liver donors, most focusing on perioperative outcomes. It is important to conduct more studies on long-term outcomes after liver donation, especially mortality and long-term liver function. Currently, we have no long-term survival data on living liver donors beyond the first seven years after donation [63].

To be able to detect any detrimental effects from living organ donation, it is important to perform studies with long enough follow-up, and an adequate control group. Based on previous studies, follow-up should be at least a decade. LDs are healthy at the time of donation. Accordingly, controls should be healthy at a similar time-point. Controls should be recruited from the same population as donors at the time of donation, and should have undergone thorough physical and biochemical evaluation. Ideally, they should be healthy enough themselves to donate an organ. If the control group is not healthy enough at baseline, this may decrease the possibility of detecting short-term and long-term risks associated with donation.

When performing cross-sectional studies, finding an appropriate control group is especially difficult. The control group should have been healthy at the time of the donor's evaluation and not necessarily at the time of study. For example, if we today were to conduct a cross-sectional study evaluating blood pressure in a group of kidney donors who donated in 2003, we would like to include controls that were of similar health in 2003. Including controls who are healthy today would make the kidney donors seem more hypertensive then they really are, and including unselected controls from the general population would conceal potential associations between donation and later increases in blood pressure. In the future, the most important focus should be on performing large studies with adequate follow-up time to enable detection of increases in mortality or other important outcomes after living donation.

13.12. References

1. The Madrid resolution on organ donation and transplantation national responsibility in meeting the needs of patients, guided by the WHO principles. *Transplantation* 2011 Jun 15;91(Suppl 11):529-31.
2. Goldfarb DA. Re: Risk of end-stage renal disease following live kidney donation. *J Urol* 2014 Sep;192(3): 827-8.
3. Cozzi DA, Ceccanti S, Cozzi F. Long-term risks for kidney donors. *Kidney Int* 2014;86(2):447.
4. IRODAT (International Registry in Organ Donation and Transplantation), website, available at www.irodat.org, accessed 9 Jul 2021.
5. *Newsletter Transplant* 2018. Available at www.edqm.eu/en/reports-and-publications, accessed 9 Jul 2021.
6. Sutherland DER, Radosevich D, Gruessner R *et al.* Pushing the envelope: living donor pancreas transplantation. *Curr Opin Organ Transplant* 2012 Feb; 17(1):106-15.
7. Kim J, Zimmerman MA. Technical aspects for live-donor organ procurement for liver, kidney, pancreas, and intestine. *Curr Opin Organ Transplant* 2015 Apr; 20(2):133-9.
8. Brännström M. Introduction: Uterus transplantation. *Fertil Steril* 2019;112(1):1-2.
9. Matas AJ, Delmonico FL. Living donation: the global perspective. *Adv Chronic Kidney Dis* 2012 Jul;19(4): 269-75.
10. Delmonico FL. A report of the Amsterdam forum on the care of the live kidney donor: data and medical guidelines. *Transplantation* 2005;79(6 Suppl.):S53-66.
11. Barr ML, Belghiti J, Villamil FG *et al.* A report of the Vancouver Forum on the care of the live organ donor:

lung, liver, pancreas, and intestine data and medical guidelines. *Transplantation* 2006;81(10):1373-85.
12. Lentine KL, Kasiske BL, Levey AS *et al.* KDIGO Clinical Practice Guidelines on the evaluation and care of living kidney donors. *Transplantation* 2017;101(8): S1-109.
13. World Health Organization (WHO). *Guiding principles on human cell, tissue and organ transplantation*, available at www.who.int/transplantation/Guiding_PrinciplesTransplantation_WHA63.22en.pdf, accessed 9 Jul 2021.
14. Abboud O, Abbud-Filho M, Abdramanov K *et al.* The Declaration of Istanbul on Organ Trafficking and Transplant Tourism. *Clin J Am Soc Nephrol* 2008 Sep; 3(5):1227-31.
15. Council of Europe Convention against Trafficking in Human Organs, CETS No. 216, available at http://conventions.coe.int/Treaty/EN/Treaties/Html/216.htm, accessed 9 Jul 2021.
16. Council of Europe Convention against Trafficking in Human Beings, CETS No. 197, available at http://conventions.coe.int/Treaty/EN/Treaties/Html/197.htm, accessed 9 Jul 2021.
17. Convention for the Protection of Human Rights and Dignity of the Human Being with regard to the Application of Biology and Medicine: Convention on Human Rights and Biomedicine, CETS No. 164, available at http://conventions.coe.int/treaty/en/Treaties/Html/164.htm, accessed 9 Jul 2021.
18. Additional Protocol to the Convention on Human Rights and Biomedicine concerning Transplantation of Organs and Tissues of Human Origin, CETS No. 186, available at http://conventions.coe.int/treaty/en/Treaties/Html/186.htm, accessed 9 Jul 2021.
19. Directive 2010/53/EU of the European Parliament and of the Council on standards of quality and safety of human organs intended for transplantation, reissued as 2010/45/EU (6 Aug 2010), available at http://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX:32010L0053, accessed 9 Jul 2021.
20. Venkat KK, Eshelman AK. The evolving approach to ethical issues in living donor kidney transplantation: a review based on illustrative case vignettes. *Transplant Rev (Orlando)* 2014 Jul;28(3):134-9.
21. Monaco AP, Morris PJ. Care of the live kidney donor: Consensus on the ultimate gift. *Transplantation*. 2005 Mar 27;79(6 Suppl):S51.
22. Human Tissue Authority. The Independent Assessment process, available at www.hta.gov.uk/guidance-public/living-organ-donation/independent-assessment-process, accessed 19 July 2021.
23. Hays RE, LaPointe Rudow D, Dew MA *et al.* The independent living donor advocate: a guidance document from the American Society of Transplantation's living donor community of practice (AST LDCOP). *Am J Transplant* 2015;15(2):518-25.
24. Biró P, Haase-Kromwijk B, Andersson T *et al.* Building kidney exchange programmes in Europe – an overview of exchange practice and activities. *Transplantation* 2019;103(7):1514-22.
25. Jendrisak MD, Hong B, Shenoy S *et al.* Altruistic living donors: Evaluation for nondirected kidney or liver donation. *Am J Transplant* 2006;6(1):115-20.
26. Guidelines for Living Donor Kidney Transplantation – British Transplantation Society, available at https://bts.org.uk/wp-content/uploads/2018/07/FINAL_LDKT-guidelines_June-2018.pdf, accessed 9 Jul 2021.
27. Directed Altruistic Organ Donation – British Transplantation Society, available at https://bts.org.uk/wp-content/uploads/2016/09/16_BTS_Directed_Altruistic_2-1.pdf, accessed 9 Jul 2021.
28. Sharif A. Directed altruistic kidney donors from overseas mask transplant tourism. *Lancet* 2015 Mar 21; 385(9973):1074.
29. European Commission. Human organ transplantation in Europe: an overview. Luxembourg: European Commission 2003, available at http://ec.europa.eu/health/archive/ph_threats/human_substance/documents/organ_survey.pdf, accessed 9 Jul 2021.
30. Resolution CM/Res (2017) 1 on principles for the selection, evaluation, donation and follow-up of the non-resident living organ donor, available at www.edqm.eu/sites/default/files/cmres_2017_1-on_principles_for_selection_eval_donation_and_follow_up_of_nrld.pdf, accessed 9 Jul 2021.
31. Cozzi E, Biancone L, López-Fraga M, Nanni-Costa A. Long-term outcome of living kidney donation: position paper of the European Committee on Organ Transplantation, Council of Europe. *Transplantation* 2016 Feb;100(2);270-1.
32. Segev DL, Muzaale AD, Caffo BS *et al.* Perioperative mortality and long-term survival following live kidney donation. *JAMA* 2010 Mar 10;303(10):959-66.
33. Mjøen G, Øyen O, Holdaas H *et al.* Morbidity and mortality in 1022 consecutive living donor nephrectomies: benefits of a living donor registry. *Transplantation* 2009;88(11):1273-9.
34. Boudville N, Prasad GVR, Knoll G *et al.* Meta-analysis: risk for hypertension in living kidney donors. *Ann Intern Med* 2006 Aug 1;145(3):185-96.
35. Garg AX, Muirhead N, Knoll G *et al.* Proteinuria and reduced kidney function in living kidney donors: a systematic review, meta-analysis, and meta-regression. *Kidney Int* 2006 Nov;70(10):1801-10.
36. Haugen AJ, Hallan S, Langberg NE *et al.* Increased long-term risk for hypertension in kidney donors – a

retrospective cohort study. *Transpl Int* 2020 May;33(5): 536-43.

37. Holscher CM, Haugen CE, Jackson KR *et al.* Self-reported incident hypertension and long-term kidney function in living kidney donors compared with healthy nondonors. *Clin J Am Soc Nephrol* 2019;14(10): 1493-9.
38. Sanchez OA, Ferrara LK, Rein S *et al.* Hypertension after kidney donation: incidence, predictors, and correlates. *Am J Transplant* 2018;18(10):2534-43.
39. Moody WE, Ferro CJ, Edwards NC *et al.* Cardiovascular effects of unilateral nephrectomy in living kidney donors. *Hypertension* 2016;67(2):368-77.
40. Garg AX, Nevis IF, Mcarthur E *et al.* Gestational hypertension and preeclampsia in living kidney donors. *Obstet Gynecol Surv.* 2015;70(5):302-3.
41. Mjøen G, Hallan S, Hartmann A *et al.* Long-term risks for kidney donors. *Kidney Int* 2014;86(1):162-7.
42. Steiner RW. The risks of living kidney donation. *N Engl J Med* 2016 Feb;374(5):479-80.
43. Steiner RW. 'You can't get there from here': Critical obstacles to current estimates of the ESRD risks of young living kidney donors. *Am J Transplant* 2019; 19(1):32-6.
44. Steiner R. GFR-related risks for kidney donors are here to stay, but what are they? *Am J Transplant* 2018; 18(10):2612.
45. Steiner RW, Ix JH, Rifkin DE, Gert B. Estimating risks of *de novo* kidney diseases after living kidney donation. *Am J Transplant* 2014;14(3):538-44.
46. Boudville N, Kanellis J. KHA-CARI commentary on the KDIGO clinical practice guideline on the evaluation and care of living kidney donors. *Nephrology* 2020;25(1):96-8.
47. Steiner RW. A very different paradigm for living kidney donor risk. *Am J Transplant* 2017;17(7):1701-2.
48. Steiner RW. More on the increased risks of young kidney donors. *Am J Transplant* 2011;11(2):413.
49. Bukabau JB, Yayo E, Gnionsahé A *et al.* Performance of creatinine- or cystatin C-based equations to estimate glomerular filtration rate in sub-Saharan African populations. *Kidney Int* 2019;95(5):1181-9.
50. Grams ME, Sang Y, Levey AS *et al.* Kidney-failure risk projection for the living kidney-donor candidate. *N Engl J Med* 2016 May 26;374(21);2094-5.
51. Lentine KL, Levey AS, Garg AX. Core assessment of predonation kidney function: clarification of the 2017 KDIGO living donor guideline. *Am J Kidney Dis* 2018 Jul;72(1):154-5.
52. Isakova T, Nickolas TL, Denburg M *et al.* KDOQI US commentary on the 2017 KDIGO clinical practice guideline update for the diagnosis, evaluation, prevention, and treatment of chronic kidney disease–mineral and bone disorder (CKD-MBD). *Am J Kidney Dis* 2017;70(6):737-51.
53. Abramowicz D, Cochat P, Claas FHJ *et al.* European renal best practice guideline on kidney donor and recipient evaluation and perioperative care. *Nephrol Dial Transplant* 2015 Nov;30(11):1790-7.
54. Gaillard F, Courbebaisse M, Kamar N *et al.* The age-calibrated measured glomerular filtration rate improves living kidney donation selection process. *Kidney Int* 2018;94(3):616-24.
55. Delanaye P, Jager KJ, Bökenkamp A *et al.* CKD: A call for an age-adapted definition. *J Am Soc Nephrol* 2019 Oct;30(10):1785-1805.
56. Denic A, Glassock RJ, Rule AD. Structural and functional changes with the aging kidney. *Adv Chronic Kidney Dis* 2016 Jan;23(1):19-28.
57. Abecassis MM, Fisher RA, Olthoff KM *et al.* Complications of living donor hepatic lobectomy – a comprehensive report. *Am J Transplant* 2012;12(5): 1208-17.
58. Iida T, Ogura Y, Oike F *et al.* Surgery-related morbidity in living donors for liver transplantation. *Transplantation* 2010;89(10):1276-82.
59. Cheah YL, Simpson MA, Pomposelli JJ, Pomfret EA. Incidence of death and potentially life-threatening near-miss events in living donor hepatic lobectomy: a world-wide survey. *Liver Transplant* 2013 May;19(5): 499-506.
60. Özbilgin M, Ünek T, Egeli T *et al.* Complications in donors using right liver graft: analysis of 280 consecutive cases. *Transplant Proc* 2017;49(3):580-6.
61. Brige P, Hery G, Chopinet S *et al.* Morbidity and mortality of hepatic right lobe living donors: systematic review and perspectives. *J Gastrointest Liver Dis* 2018; 27(2):169-78.
62. Trotter JF, Adam R, Lo CM, Kenison J. Documented deaths of hepatic lobe donors for living donor liver transplantation. *Liver Transplant* 2006;12(10):1485-8.
63. Muzaale AD, Dagher NN, Montgomery RA *et al.* Estimates of early death, acute liver failure, and long-term mortality among live liver donors. *Gastroenterology* 2012;142(2):273-80.
64. Pomfret EA. Early and late complications in the right-lobe adult living donor. *Liver Transplant* 2003;9(10 Suppl. 2):S45-9.
65. Egawa H, Teramukai S, Haga H *et al.* Impact of rituximab desensitization on blood-type-incompatible adult living donor liver transplantation: a Japanese multicenter study. *Am J Transplant* 2014;14(1):102-14.
66. Goss MB, Rana A. ABO-incompatible liver transplantation: is it a viable option with modern innovation? *Clin Liver Dis* 2017;10(5):124-9.
67. Mohite PN, Popov AF, Yacoub MH, Simon AR. Live related donor lobar lung transplantation recipients

surviving well over a decade: still an option in times of advanced donor management. *J Cardiothorac Surg* 2013;8(1):37.

68. Yusen RD, Hong BA, Messersmith EE *et al.* Morbidity and mortality of live lung donation: results from the RELIVE study. *Am J Transplant* 2014;14(8):1846-52.
69. Lam NN, Schnitzler MA, Segev DL *et al.* Diabetes mellitus in living pancreas donors: use of integrated national registry and pharmacy claims data to characterize donation-related health outcomes. *Transplantation* 2017;101(6):1276-81.
70. Benedetti E, Holterman M, Asolati M *et al.* Living related segmental bowel transplantation: from experimental to standardized procedure. *Ann Surg* 2006; 244(5):694-9.
71. Brännström M, Johannesson L, Bokström H *et al.* Livebirth after uterus transplantation. *Lancet* 2015; 385(9968):607-16.
72. Nordheim E, Olafsson Storrø M, Natvik AK *et al.* Donor-derived strongyloidiasis after organ transplantation in Norway. *Transpl Infect Dis* 2019;21(1):e13008.
73. Muzaale A, Kucirka L, Massie A *et al.* Risk of end-stage renal disease in HIV-positive potential live kidney donors. *Am J Transplant* 2017 July;17(7):1823-32. https://doi.org/10.1111/ajt.14235.
74. Infectious diseases of specific relevance to newly-arrived migrants in the EU/EEA. European Centre for Disease Prevention and Control, 23 November 2015. Stockholm: ECDC, 2015, available at www.ecdc.europa.eu/en/publications-data/infectious-diseases-specific-relevance-newly-arrived-migrants-eueea, accessed 10 Jul 2021.
75. World Health Organization. *Global health atlas*, available at www.hrhresourcecenter.org/node/549.html, accessed 10 Jul 2021.
76. Gross CR, Messersmith EE, Hong BA *et al.* Health-related quality of life in kidney donors from the last five decades: results from the RELIVE study. *Am J Transplant* 2013;13(11):2924-34.
77. Clemens KK, Thiessen-Philbrook H, Parikh CR *et al.* Psychosocial health of living kidney donors: a systematic review. *Am J Transplant* 2006 Dec;6(12):2965-77.
78. Dew MA, Jacobs CL, Jowsey SG *et al.* Guidelines for the psychosocial evaluation of living unrelated kidney donors in the United States. *Am J Transplant* 2007 May;7(5):1047-54.
79. Olbrisch ME, Benedict SM, Haller DL, Levenson JL. Psychosocial assessment of living organ donors: clinical and ethical considerations. *Prog Transplant* 2001; 11(1):40-9.
80. Dew MA, Dimartini AF, Devito Dabbs AJ *et al.* Preventive intervention for living donor psychosocial outcomes: feasibility and efficacy in a randomized controlled trial. *Am J Transplant* 2013;13(10):2672-84.
81. Jowsey SG, Jacobs C, Gross CR *et al.* Emotional well-being of living kidney donors: findings from the RELIVE study. *Am J Transplant* 2014;14(11):2535-44.
82. Schweitzer J, Seidel-Wiesel M, Verres R. Donor-recipient interaction: the Heidelberg model of evaluation and consultation. *Nephrol Dial Transplant* 2004 Jul;19(Suppl 4):iv75-8.
83. Rodrigue JR, Hanto DW, Curry MP. Patients' expectations and success criteria for liver transplantation. *Liver Transplant* 2011;17(11):1309-17.
84. Dew MA, Jacobs CL. Psychosocial and socioeconomic issues facing the living kidney donor. *Adv Chronic Kidney Dis* 2012 Jul;19(4):237-43.
85. Rodrigue JR, Fleishman A, Vishnevsky T *et al.* Development and validation of a questionnaire to assess fear of kidney failure following living donation. *Transpl Int* 2014;27(6):570-5.
86. Council of Europe Council of Ministers, Resolution CM/Res (2015) 11 on establishing harmonised national living donor registries with a view to facilitating international data sharing, available at www.edqm.eu/en/legal-framework, accessed 10 Jul 2021.
87. Living Donor Observatory (Lidobs). Recommendations for high quality practices in living donation. International Conference on Living Donation, Barcelona (Spain), 6-7 Nov 2014, available at http://wp2.eulivingdonor.eu/wp-content/uploads/2015/08/FINAL-Lidobs-Consensus-Leaflet.pdf, accessed 10 Jul 2021.
88. Opelz G, Morath C, Süsal C *et al.* Three-year outcomes following 1420 ABO-incompatible living-donor kidney transplants performed after ABO antibody reduction: results from 101 centers. *Transplantation* 2015;99(2):400-4.
89. Scurt FG, Ewert L, Mertens PR *et al.* Clinical outcomes after ABO-incompatible renal transplantation: a systematic review and meta-analysis. *Lancet* 2019; 393(10185):2059-72.
90. de Weerd AE, Betjes MGH. ABO-incompatible kidney transplant outcomes: a meta-analysis. *Clin J Am Soc Nephrol* 2018;13(8):1234-43.
91. Hall EC, Engels EA, Montgomery RA, Segev DL. Cancer risk after ABO-incompatible living-donor kidney transplantation. *Transplantation* 2013;96(5): 476-9.
92. Haririan A, Nogueira J, Kukuruga D *et al.* Positive cross-match living donor kidney transplantation: longer-term outcomes. *Am J Transplant* 2009;9(3): 536-42.
93. Bentall A, Cornell LD, Gloor JM *et al.* Five-year outcomes in living donor kidney transplants with a positive crossmatch. *Am J Transplant* 2013;13(1):76-85.
94. Montgomery RA, Lonze BE, King KE *et al.*

Desensitization in HLA-incompatible kidney recipients and survival. *N Engl J Med* 2011;365(4):318-26.

95. Morath C, Beimler J, Opelz G *et al.* Living donor kidney transplantation in crossmatch-positive patients enabled by peritransplant immunoadsorption and anti-CD20 therapy. *Transpl Int* 2012;25(5):506-17.

96. COST (European Cooperation in Science and Technology). European Network for Collaboration on Kidney Exchange Programmes, available at www.enckep-cost.eu, accessed 10 Jul 2021.

97. Yabu JM, Pando MJ, Busque S, Melcher ML. Desensitization combined with paired exchange leads to successful transplantation in highly sensitized kidney transplant recipients: strategy and report of five cases. *Transplant Proc* 2013;45(1):82-7.

98. Rees MA, Kopke JE, Pelletier RP *et al.* A nonsimultaneous, extended, altruistic-donor chain. *N Engl J Med* 2009;360(11):1096-101.

Chapter 14. **Paediatric donation**

14.1. Introduction

The death of a child is the end of a tragedy that leaves parents defenceless as they face the painful loss of their most precious gift: their child [1]. During the grieving process parents may cling to their relationship with the dead child [2]; for some, the donation of their child's organs provides great comfort with and acceptance of their loss. Healthcare providers (HCPs) offer donation as part of a sensitive plan aimed at helping reconstruct parents' lives in a new reality, as well as creating a lasting legacy for their child. However, paediatricians may feel uneasy when confronting the death of a child under their care. Emotional factors and unfamiliarity with paediatric donation and transplantation procedures often prevent them from referring a possible donor, thus losing the opportunity to help grieving parents and to help patients in need of a life-saving or life-changing organ transplant.

The Global Observatory on Organ Donation and Transplantation – managed by the Spanish Organización Nacional de Trasplantes (ONT), as collaborating centre of the World Health Organization [3] – reports important variations in the number and rate of paediatric deceased organ donors (< 18 years of age) across countries (see Figure 14.1).

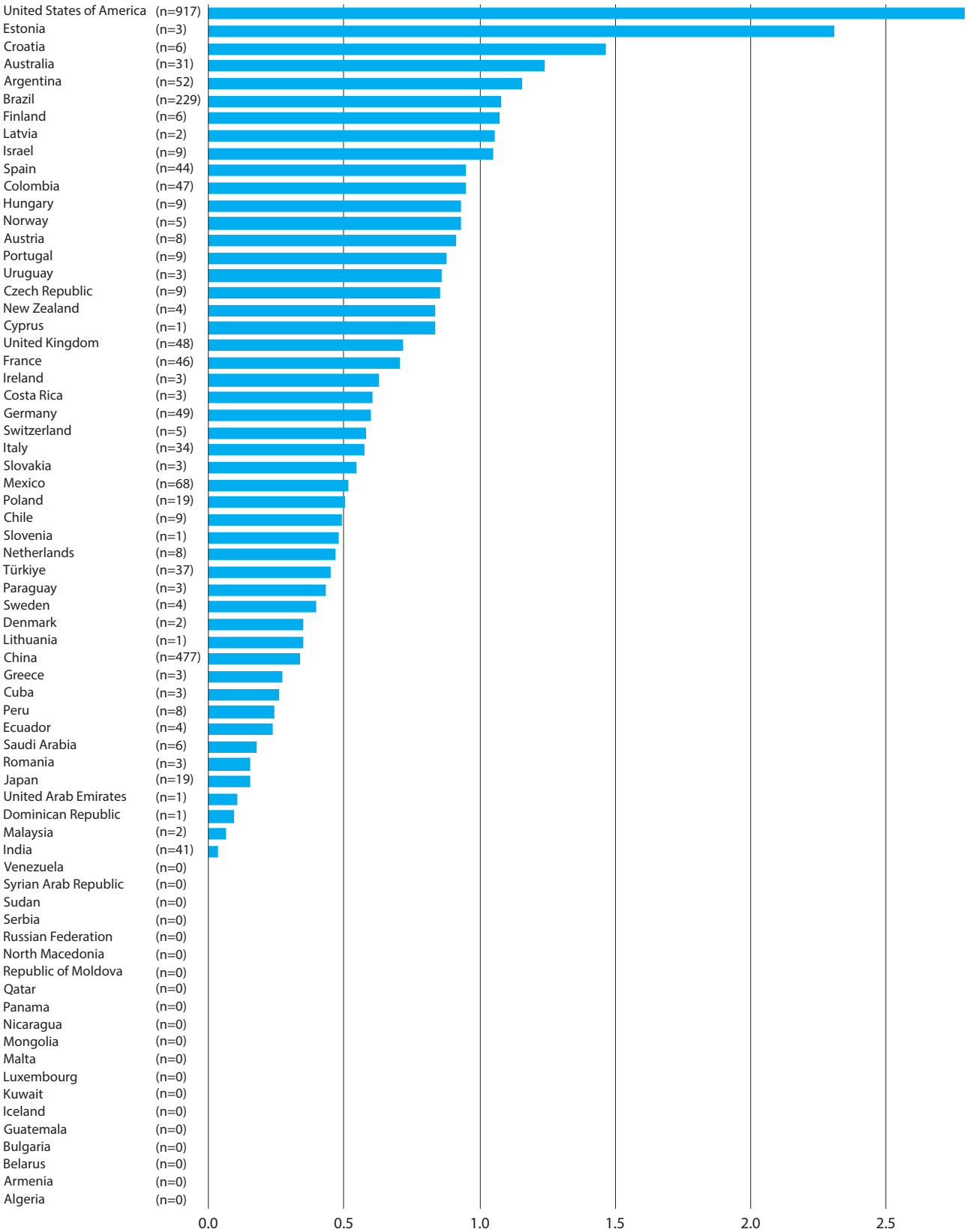
Children represent a true minority among deceased donors. Indeed, paediatric donation represents a small but invaluable portion of the deceased donor pool, comprising roughly 2 % to 8 % of deceased donors in some of the organisations with the highest rates of cadaveric donation (Spain [4], United States [5], France [6], the United Kingdom [7], Australia [8] and Eurotransplant countries [9]). In contrast, children comprise about 1.5 % of the waiting list for transplantation in the US and in Eurotransplant countries, 2 % in the UK, 3 % in Australia and 6 % in Spain [10].

There is no international consensus defining the age of a paediatric donor, resulting in discrepancies in the published donation rates: in the United States, United Kingdom and France, paediatric donors are those in the range 0 to 17 years; in Spain and the countries involved in Eurotransplant, paediatric donors are those aged less than 16 years, and in Australia the age of paediatric donors ranges from birth to 14 years [4-9]. This lack of a standard definition for paediatric donors limits data acquisition and the ability of researchers and stakeholders to clearly understand paediatric deceased donation performance [11].

This chapter aims to clarify some aspects of paediatric deceased organ donation, from birth to 18 years, focusing on:

1. the importance of paediatric deceased organ donation,
2. donation after the neurological determination of death, i.e. brain death (pDBD),
3. donation after the circulatory determination of death (pDCD),
4. donation in special circumstances (neonates with anencephaly, use of normothermic regional perfusion, etc.),
5. the transplantation of organs recovered from paediatric donors.

Figure 14.1. **Absolute number (in brackets) and rate per million population of actual paediatric deceased organ donors (< 18 years of age) in 2019**



Source: Global Observatory on Organ Donation and Transplantation, www.transplant-observatory.org/ (data provided upon direct request).

This chapter is intended for paediatricians and HCPs directly involved in the deceased paediatric donation process with the objective of enhancing or increasing involvement of the medical team and helping parents pursue organ donation for their child [12].

14.2. The importance and particular features of paediatric deceased organ donation

Medical societies, such as the American Academy of Pediatrics [13] and The Transplantation Society [10], encourage physicians – specifically paediatricians and neonatal critical care specialists – to recognise the importance of organ donation and to establish and follow donation protocols and best practices to identify, medically manage and recover organs for transplantation from potential paediatric donors. Policy makers, stakeholders and physicians should work together in shaping practices and procedures that provide equitable allocation of organs for their paediatric and adult patients.

Discussion of paediatric donation can be challenging for many HCPs. The emotional loss of a child for parents, the responsibilities of the medical team and their views of the patient's best interests may result in misconceptions about what parents may want to do or consider doing from altruism to help other families. This can lead to disturbed attitudes towards donation, affecting identification of possible donors and absence of timely notification to the donor co-ordinator (DC) or staff of the organ procurement organisation (OPO). Donation programmes may suffer from fewer donors and fewer opportunities to recover organs for transplantation [10, 14].

Paediatric donation has unique challenges and complexities:

- Annually thousands of children and adults receive an organ from a deceased donor [15], but paediatric patients have fewer transplantation opportunities, mostly due to fewer paediatric donors, size matching and technical challenges with transplantation of smaller organs. These factors can result in a higher mortality rate than that observed in the adult population [10]. Data about paediatric patients on the waiting list remain inaccurately quantified or unacknowledged as a result of the lack of international records and the absence of criteria defining clinical status that make listed children ineligible for transplantation [5, 8, 11-12, 14].
- Overall mortality of children is low [16-17] and death rates have been declining since the start of the 21st century because of improved medical therapies, eradication of life-threatening infectious diseases and the use and refinement of passenger safety-restraint systems. Additionally, the care provided in modern paediatric intensive care units (PICUs) has significantly improved the chances of survival for children with a life-threatening disease [18]. This means that the potential for paediatric donation is expected to be limited.
- The number of pDBD donors has remained relatively stable during the last decade. Although DBD donors continue to provide the vast majority of organs for transplantation, they seem insufficient to reach the currently increasing demands of paediatric and adult transplantation. Also, weaknesses in data identification and referral of potential paediatric DBD donors suggest missed donation opportunities [19]. This emphasises the need to provide ongoing education to HCPs and non-healthcare providers about considering organ donation when children are facing end-of-life issues [20].
- Decisions whether to withhold, withdraw or limit life-sustaining treatment in children with life-limiting or life-threatening illness may be difficult, contentious and emotionally charged. HCPs may require specific training and will need to understand religious and cultural beliefs of families as they come to terms with the death of their child.
- Early referral to the donor co-ordinator or staff of the OPO is best practice to increase potential for organ donation since it allows the timely assessment of the possible donor [20]. Children may suffer from rare diseases such as inborn errors of metabolism, chromosomal abnormalities or anatomic defects that may require the knowledge of experts in the field of paediatrics to collaborate with the DC or OPO and make a determination of donor suitability [21-22].
- When considering DCD from a paediatric or neonatal patient, the DC/OPO and medical team should assess the patient for organ donation potential and the probability of circulatory arrest within a specified time period following withdrawal of life-sustaining treatment (WLST) [23].
- Size matching can be difficult, especially for very young or low-weight donors and is a common reason that paediatric organs are not transplanted [23]. This is especially true for those children awaiting a thoracic organ for

transplant. Damage to organs during procurement can render organs unsuitable for transplantation. Medical examiner and coroner denials for donation also exist, limiting recovery of organs for transplantation [21].

- Many transplant teams may rule out neonatal organs because of their small size and immaturity, which could lead to graft dysfunction or failure. Transplantation experience with organs from neonatal DCD donors is very limited but organs have been recovered and transplanted with success [20-21].

Despite the challenges encountered with the paediatric donation process, many lives continue to be saved by recovery of organs from paediatric donors. There still exists room for improvement in DBD and DCD.

14.3. Donation as part of paediatric end-of-life care: ethical aspects

Offering organ and tissue donation as an option to be included in end-of-life (EOL) care plans is a clinical practice that is recommended by several medical societies – in view of the overall best interests of the dying patient and their family [12, 24-28]. Paediatric organ donation is unique as children cannot make a decision about donation and must rely on parents or guardians to authorise organ and tissue donation ('family-centred care').

Discussions about organ donation with guardians/parents of children facing EOL issues should be a collaborative effort between the HCP and the DC/OPO staff, once medical contraindications have been ruled out. Although the child may not benefit from organ donation, donation can help with the parents' healing process by allowing the legacy of their child to live on in another person through the gift of organ donation.

When providing EOL care, the child's best interests must be paramount, with due consideration of the principles of beneficence (promoting welfare) and nonmaleficence (minimising harm). Such interests include any previously expressed preferences of the child regarding donation when these are known [29] and provision of optimal care at the end of life – which become ethical duties of HCPs caring for dying patients. While first person donation intent will rarely be known for children, some jurisdictions allow minors to register non-binding consent for donation in 'intent to donate' registers. Optimal care at the end of life also encompasses a duty not to offer or implement futile interventions and to withdraw interventions when they become futile. These discussions must occur with the parents, who ultimately will consent to procedures or authorise donation. Families should be assured that the cessation or withdrawal of interventions when deemed no longer helpful to prolong life does not mean withdrawal of care for the child. EOL care must include the management of the child's symptoms, including pain and suffering, as well as provision of emotional and spiritual support to the child and family [30-31]. Organ donation cannot take precedence over quality EOL care.

14.4. Actual and potential paediatric organ donation

A limited number of published studies have assessed the potential of neonatal and paediatric donation [18, 21, 23, 32-39]. Mortality rates in PICUs average 2 % to 4 % of all admissions. The majority of patients who die in an ICU (children and adults) die following WLST because this is no longer considered beneficial to the patient. Recent PICU studies show that 10 % to 20 % of dying patients meet brain death criteria and about 50 %-70 % die after WLST [18, 32, 36-39].

14.4.1. Donation after the neurological determination of death

The majority of paediatric organs recovered for transplantation derive from DBD donors [4-9]. Organ donation following the neurological determination of death varies significantly according to countries, regions and hospital characteristics. In the United States, four studies carried out in different areas (tertiary hospital with a paediatric trauma centre, seven affiliated hospitals and a multicentre database including 150 institutions and 15 344 patients who died in PICUs) showed the percentage of patients who die in conditions consistent with brain death varies from 10 % to 20 %, with conversion rates into actual organ donors of 45 % to 78 % [18, 32, 36 and 37]. As expected, there is a linear association between PICU size (less than 500 patients per year *versus* 2 000 to 4 000 patients per year) and the number of brain-dead patients per year (5 times in a year in smaller units and a mean of 10 times per year in larger units) [37].

The estimated percentage of PICU deaths potentially suitable for DBD donation in Spain [38-39], Australia [40], and the Netherlands [33] is 11 % to 15 %. In Spain, the quality assessment programme

carried out by the ONT (data collected in 1999-2011) found that 11.3 % of children who died in the PICU met clinical conditions consistent with BD. Of these, 42 % became actual donors, a conversion rate that contrasts with the 56 % of the adult potential DBD donors [39]. Reasons for a decreased conversion rate among paediatric *v.* adult potential DBD donors were a higher percentage of losses due to medical unsuitability (28.1 % *v.* 22.5 %; $p < 0.001$), haemodynamic instability or cardiac arrest during potential donor management (5.7 % *v.* 2.6 %; $p < 0.001$), lack of suitable recipients (2.3 % *v.* 0.6 %; $p < 0.0001$) and logistical issues (1 % *v.* 0.4 %; $p = 0.003$). No significant differences were observed in losses due to declined consent or judicial authorisation. Moreover, only two paediatric cases were lost due to the inability to complete the diagnosis of BD.

The National Health Service of the UK annually performs potential donor audits of all PICUs to determine their potential for organ donation. The audit report for 2015-16 shows that, despite clear standards that if brain death is suspected then brain death testing should be performed, the rate of neurological determination of death in PICUs is 71.7 %, compared with 84.5 % overall (adult and paediatric data combined), demonstrating scope for improvement. Although some PICUs have rates of testing that match best practice, in others neurological testing is never applied [21].

14.4.2. Donation after the circulatory determination of death

The rates of DBD donation in children have remained largely stagnant in the past 10 years. However, there is evidence of an increasing number of DCD practices in the US [5], Australia [8] and some western European countries [15], indicating a change in the pattern of deceased donation that also affects paediatric deceased donation.

Paediatric DCD is estimated to increase paediatric deceased donation by 20 % to 58 % in countries with similar child mortality rates [41]. Although the definition of a potential donor varies according to the researchers' criteria, in the study by Weiss *et al.* it is estimated that the potential for pDCD is around 9 %-20 % in PICUs and 8 %-36 % in neonatal intensive care units (NICUs) [41].

In a published review, the estimated number of potential DCD donors at a children's hospital with a level 1 trauma programme exceeded the potential DBD donors when donor 'suitability' (lack of exclusion criteria for donation, i.e. cancer and systemic infection) and time to death after WLST were evaluated by the OPOs. The clinicians participating in the study failed to refer possible organ donors to the local OPO in 23 % of the cases where the decision of WLST had been made, with a non-referral rate of 39 % for children aged 1 week to 1 month. Paediatric DCD increased the number of donors in the centre by 67 % and the number of organs suitable for transplantation by 42 % [32].

The review by Hawkins *et al.* of paediatric and neonatal organ donation in the UK shows that the rate of referral of potential DCD donors from PICUs was 72 %, compared with 83 % for potential donors of all ages. Many contributory factors to missed referral opportunities were identified, including missed identification of possible donors, perceived medical unsuitability and unclear disease processes leading to death [21].

A prospective multicentre study in Spanish hospitals about the circumstances of death of children who died in 18 PICUs, including 14 051 admissions over a 2-year period (2017-18), recorded a total of 250 deaths. Of these, 122 (49 %) died after the decision of WLST, 71 (28 %) died after providing paediatric advanced life support, and 57 (23 %) met BD criteria. The most common form of WLST was termination of mechanical ventilation (52, 23 %). The decision for donation after WLST was requested in a very small percentage of cases (15 % of all WLST) [38]. DCD in Spain is already well established in adult ICUs, but not in PICUs. According to data from the ONT, from 2010 to 2020 a total of 478 paediatric donors (aged < 18 years) were reported; 449 were potential DBD (94 %) and 29 potential DCD donors (6 %). Whereas 92 % of potential DBD donors transitioned to actual organ donors, only 39 % of the potential DCD donors became actual donors – in 51 % of the cases because of the lack of an adequate recipient [4]. In view of the need to further develop pDCD, Spain has recently issued guidance to optimise paediatric donation, including pDCD [42].

In a retrospective study carried out in Australia and New Zealand over 15 years (2000 to 2015), there were 267 paediatric organ donors, representing 5 % of all actual donors. The rate of paediatric organ donors as a percentage of ICU deaths was comparable to adults (6.0 % *v.* 5 %). Over the entire period, pDBD represented 91 % and pDCD 9 %. They remark that pDCD increased from 0.7 % to 17 % between the two time periods (2000-07 *v.* 2008-15). Children younger than 2 years of age had a lower rate of donation than the general paediatric cohort (1.2 % *v.* 6.0 %) [40].

A report of the UK, Spain and the US, recording the paediatric organ donation national data from 2011 to 2015 (inclusive), shows a substantial variation in

paediatric donation rates and practice between countries, highlighting a large margin for improvement, where undoubtedly the production of a rigorous clinical practice guideline for paediatric organ donation would be beneficial [11, 24].

14.4.3. Neonatal donation

Neonatal donation is an area of increasing interest in terms of potential for organ donation [21, 23, 34, 43]. Despite established criteria for the determination of death by neurologic criteria in term neonates [44-45], organ and tissue donation rarely occur in this population.

Many critically ill neonates die in the NICU after WLST interventions [46], but organ donation is infrequently considered, resulting in a missed opportunity for pDCD. Depending on gestational age and weight, infants between 1 week and 1 month of age are usually not considered for DCD donation after WLST. Fewer than 1 % of all organ or tissue donations come from this population of neonatal donors [32].

Recently, two studies observed that 8 %-10 % of NICU deaths were eligible candidates for pDCD [23, 43]; pDCD provides opportunity for organ donation from neonates that do not meet BD criteria [5, 10, 15, 23, 32, 34, 43].

Published case reports show that children aged 2 months or younger may become DBD and DCD donors, but their real contribution to the donation potential is far from being reached [34].

As we mentioned previously, many transplant teams may rule out neonatal organs because of their small size and immaturity. Although the transplantation experience with organs from neonatal DCD donors is very limited, the use of *en bloc* kidneys has had successful outcomes [20-21, 47]. Procurement of other organs has been more contentious [48]. Hearts recovered from neonatal DCD donors have been transplanted with good outcomes [24, 49-50]. Livers recovered from neonatal donors are being used for liver cell transfusion therapy in infants and children in metabolic diseases of the liver [51-52].

14.5. The paediatric organ donation process

Organ donation remains an uncommon event for children who die in PICUs [11]. The opportunity to proceed with organ donation requires a complex alignment of medical, legal, ethical and logistical factors involving families, patients, clinicians, hospital executive officers and DC or OPO staff.

Despite the well-recognised value of saving and improving lives through organ transplantation, families and HCPs may perceive elements of the donation process as ethically challenging during EOL care. These ethical challenges can occur during patient management, and especially in the context of pDCD [30, 53]. Unfounded parental hopes of recovery and survival, and fears that cessation of futile interventions may result in WLST for their child, may underpin reluctance to consider donation [30, 54]. Concerns about harming potential donors or their families through discussion of donation, use of interventions to preserve donation opportunities or recovery of organs after death is declared, may discourage health professionals from enabling donation opportunities [53]. These apparent conflicts between the interests of a potential donor and their family and the benefits anticipated from donation may result from inadequate communication between staff and family [10].

The process of organ donation relies on identification of a possible donor, referral to the co-ordination team or OPO staff, determination of death, consent/authorisation for donation, donor management and the recovery of organs. Each stage requires ideal attention to the preceding task, and at each step performance problems as well as unavoidable issues can lead to loss of possible donors [21]. Fully informed consent/authorisation, the intensive care team's understanding of every step of the donation process and DC/OPO engagement are all essential to eliminate confusion that could ultimately disrupt or affect donation and organ recovery and derail the expressed wishes of the child and/or parents.

Obstacles to the recovery of organs from donors include:

a. family or cultural resistance to organ donation,
b. issues related to authorisation or consent of families (including inappropriate timing and confusion about the death of their child),
c. medical staff perceptions and misunderstanding about organ donation,
d. missed opportunities for donation (including medical examiner denials in child abuse cases) and
e. inadequate donor management resulting in loss of viable organs for transplantation [20].

14.5.1. Identification and routine referral of possible donors

Compared to adult ICUs, PICUs and NICUs far less often offer organ donation (for more detail, see §14.4).

Identification of a possible donor is the first and most important phase of the donation process. The

HCP should acknowledge and be alert to detect and refer all children in ICUs to the DC or OPO staff in a timely manner, regardless of the bedside clinician's perception of donation eligibility. Common clinical triggers include neurologic injury that may proceed to BD, or after a decision on WLST is being made. Opportunities for donation are often lost during WLST in PICUs, mostly because of late notification to the DC or OPO.

Reasons that have been described for failure to identify a possible donor are:

a. absence of universal clinical criteria to identify all potential deceased donors,
b. lack of information on the best clinical trigger for donor identification [22],
c. donation not considered with no documented reason,
d. considered to be medically unsuitable,
e. BD not confirmed,
f. family declined donation after BD or following a decision of WLST, or
g. medical contraindications (infection, malignancy, organ dysfunction, genetic syndrome, size < 2 kg, unstable haemodynamic status) [55].

According to the UK and Spanish guidelines on paediatric donation "Where donation is likely to be a possibility, full consideration should be given to the matter when caring for a dying patient". Missing donation opportunities may dishonour the parents' wishes and frustrates the opportunity for patients on the waiting list [42, 55].

Assessment of the donor potential should be determined using established guidelines and coordinated with a DC or the OPO. The use of clinical triggers or other methods to facilitate prompt identification of all possible donors, in conjunction with a policy of required referral, will help to improve performance in the process of paediatric donation [22] (for more detail, see Chapter 2).

With the objective of estimating the potential of paediatric deceased donation and to evaluate performance in the donation process, systematic audit of all potential donors should also occur in PICUs and NICUs, to ensure accountability and responsibility for all providers involved in the donation process [10, 21, 33, 39, 56].

14.5.2. Approach: offering organ donation to family

Assessment of potential paediatric donors may be complex, and an approach to family should be systematically planned [10].

As a general rule, conversations about WLST must be previous and independently held by the paediatricians most responsible for the child, assuring the decoupling of the prognostic information and organ donation [25]. However, strict separation may be in certain circumstances unnecessary. According to the Canadian Guidelines, "When the likelihood of surviving is very low and parents are inclining to organ donation, continuing life support might end in failed cardiopulmonary resuscitation while WLST may successfully end in pDCD" [57].

While the positive influence of the DC or the OPO staff as leader when approaching the family of a child has not been confirmed in randomised clinical trials [58], several observational studies show increased response rates when the approach is done by a specific trained professional. Hence, the DC or OPO staff should work in a collaborative manner with the medical team when approaching families to discuss donation opportunities [59-63] (for more detail, see Chapter 4).

According to the idiosyncrasies of each transplantation system worldwide, the DC background and professional profile will be different. However, every system should dedicate efforts in training HCPs to proactively address every donation process compassionately, following the cultural roots and religious beliefs of the family.

Respect for parental autonomy in decision making on donation should be guaranteed. HCPs should not fail to approach parents because of their own assumption that parents will feel worse or deny donation.

14.5.3. Consent or authorisation

First person authorisation is not possible in young children, so parents or the legal guardian must provide authorisation for their child to become an organ donor [57, 64]. In the case of countries with an opting-out system, inclusion in a non-donor registry by parents will allow their child to be excluded from becoming a donor.

The 'best interests' standard does not apply in paediatric donation as most children have never expressed an opinion on donation and cannot be benefited or harmed as a result of donation once death has occurred [12].

The 'substitute judgement' standard for paediatric donation has some nuances, since parents will decide upon the values and welfare of the whole family in a model of family-centred best interests. While adult interests about donation are viewed on the basis of their own beliefs and medical benefit,

paediatric donor interests are composed of what parents consider is best for the family's welfare (societal, emotional and religious) [25]. As a family member, the potential donor would have been raised following their parent's solidarity values, presumably embracing them as part of their education.

However, should the child express concerns regarding donation, even if not competent to provide authorisation, their opinion must be respected [12].

14.6. Determination of death by neurologic criteria in children

Neurologic determination of death for a child is a rare event in any PICU or NICU. Few diagnostic procedures carry such a fundamental outcome. Making this determination means the suspected death of a child becomes a reality for everyone, especially the parents, and that continuation of invasive life-sustaining treatment is no longer appropriate, unless there is authorisation for organ donation.

Organ donation still predominantly occurs following BD, despite the last decade's increase in DCD in adults, and in many countries in children. However, in some European countries DCD is not possible yet for a variety of reasons, so the only mode of donation occurs after BD.

The medical literature supports widespread professional and public acceptance of the verification of human death using neurological criteria [65], but international diversity exists in how neurological death is determined [66-71]. Isolated development of national guidance, in Europe and elsewhere, has led to this clinical diversity, which is particularly obvious in children, and clearest in infants. This variability includes the philosophical basis of 'brain death', the age at which verification using neurological criteria is permitted, the actual process to determine BD, the requirement and type of ancillary study, and the number of and time interval between examinations necessary before death can be verified.

Despite such differences, there are arguments that the similarities far outweigh the conceptual and – weakly evidenced – practical differences in ancillary studies and examination intervals to determine BD. Indeed, even with the fundamental differences in the philosophical underpinning of the 'whole brain-death' concept and the 'brainstem death' concept, the practical bedside determination of death is remarkably similar [66, 72]. The concept of 'whole brain death' is almost uniformly accepted in European countries, with the well-known exception of the UK 'brainstem-death' concept [71-73] (for more detail, see Chapter 3).

14.6.1. Neurological determination of death or brain death

BD in children, as in adults, is a clinical diagnosis based on the triad of coma/persistent unconsciousness, absent brain stem reflexes and apnoea (lack of response to significant hypercarbia) with a known cause of brain injury, and in the absence of confounding factors in a patient maintained on invasive mechanical ventilation. Ancillary studies, which vary by jurisdiction, can assist with determination of BD.

Data from currently unpublished research highlights European variability in the determination of death by neurologic criteria, which is considered feasible at various thresholds of age, starting from premature infants (< 37 weeks of gestational age) in Spanish guidelines (S); term neonates (≥ 37 weeks of gestational age) in Belgian (B), German (D), French (F), Poland (P) and United Kingdom (UK) guidelines, or > 7 days of life in Austrian (A) guidelines; and the post-neonatal period (> 1 month) in Swiss (CH) guidelines, or up to 1 year, in Danish (DK) guidelines, if defined at all (in 7/9) [74-84] (Appendix 4). The US paediatric guidelines for BD include the criteria used in children from 37 weeks gestational age to 18 years of age [85].

Beyond the neonatal period, neurological determination of death can be performed in young infants (with relevant amendments to the diagnostic procedures in adults and older children) of either > 1- or 2-months corrected gestation months (UK, F, P) to 1 year (B, CH, DK) or 2 (A, D, S) and even 3 (Hungary) years of age (see Appendix 4) [74-84].

A set of clinical features for the determination of death by neurologic criteria unanimously comprises absent response to stimuli (coma), absent pupillary reactivity, ocular motility, corneal, gag and cough reflexes, rooting reflexes in infants and finally persistent apnoea despite profound hypercarbia.

Stringent prerequisites in all countries are:

a. known aetiology of the underlying cerebral lesion,
b. absence of any reversible cause of unconsciousness including sedative and paralytic agents, metabolic disturbances, toxins or ingestions, though to various confirmatory degrees (e.g. drug levels must be obtained in 3/10 countries assessed; see Appendix 4),
c. end organ failure,
d. normotension,
e. mild hypo- to normothermia (34 to 36 °C, but > 32 °C in B).

Clinical examination and testing is almost

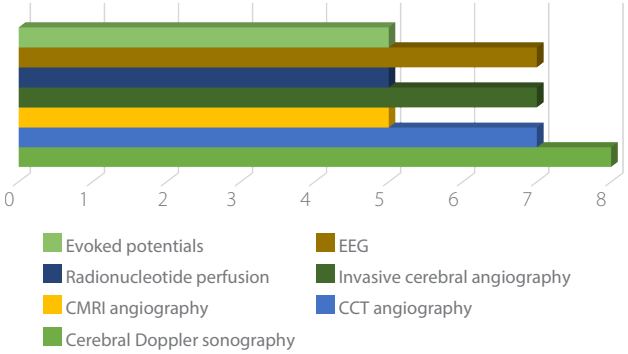
uniformly performed by two (or more) clinicians (intensive care specialists – sometimes mandated paediatricians – or specialists in neurology/neuro-surgery mandatory in 4/10 or 6/10 countries respectively; see Appendix 4) [71, 74-84].

In neonates and infants beyond the neonatal period, repeated clinical examination is mandatory with an observational period between consecutive clinical tests, which ranges from 12 to 72 hours, depending on country and/or the type of cerebral lesion. An ancillary or 'confirmational' study is recommended in specific cases (e.g. impossibility to conclude the clinical diagnosis, infratentorial lesions) in only 7 of 9 countries, but is already compulsory in D and F; see Appendix 4) [71, 74-84].

Ancillary testing (if applied) can be either functional (EEG, evoked potentials) or based on cessation of cerebral perfusion (Doppler-sonography 20, CT-angiography, MRI-angiography, radionucleotide perfusion assays or invasive cerebral angiography). Independently of age, a confirmatory test is mandatory in France, either EEG or cerebral angiography (which is recommended < 2 months), whereas Swiss guidelines rely on cerebral perfusion testing only. In small infants (< 2 years of age) German guidelines require repeated clinical examinations to be confirmed by ancillary testing (choice is lesion-related or is left to institutional and personal preferences); others consider ancillary studies an appropriate substitute for (shortening) the observational period (see Figure 14.2, Appendix 4) [74-84]. The US recommendations for the determination of death by neurologic criteria specify that ancillary studies are not required and should not be viewed as a substitute for the neurologic examination. Ancillary studies are used to 'complement' the clinical examination, with continued emphasis that BD is a clinical diagnosis. The use of ancillary studies is usually reserved for situations where a full clinical examination and apnoea test cannot be completed and where there is a high probability that the person is, in fact, dead by neurologic criteria [71, 85]. A recent amendment to the UK guidelines after an extensive literature search judged ancillary studies neither mandatory nor recommended in 'newborns' up to 2 months of age (except when clinical diagnosis cannot be achieved) "due to insufficient specificity and sensitivity" [84]. BD can be determined for infants and children supported by extracorporeal membranous oxygenation (ECMO; see §14.7.3.10) [71].

Detailed information about ethical issues and the need to standardise worldwide criteria for BD determination can be found in Chapter 3.

Figure 14.2. **Ancillary tests (either obligatory or optional) used for neurological determination of death in 10 European countries**



Source: Modified from data supplied by Petry A; Lücking KM; Krüger M (unpublished data).

14.7. Intensive care management of the potential paediatric organ donor

Progression to BD due to certain illnesses or severe trauma occurs in patients of all ages with an associated ICU pathway of variable duration after admission [19, 38]. Complex systemic complications of BD include inflammatory, haemodynamic and endocrine alterations. Therapeutic options for medical treatment of adults have been the subject of many publications (for more detail, see Chapter 5), with considerably less written about our paediatric population. Consequently, several of the recommendations and guidelines on the management of these deleterious physiological changes in potential organ donors pertain mainly to adult care, with limited guidance for paediatric care [86-89].

Early and aggressive management of the systemic effects of BD in both adults and children has increased the number of organs recovered and their quality for transplantation [90-92]. The possibility of paediatric organ donation is vital and should be explored in a collaborative manner with the DC or OPO staff, while rigorously applying best principles for the medical management of a potential organ donor and observing the ethical and legal directives of BD [93].

To minimise the organic and metabolic disorders due to pathophysiological derangements from BD, which are often rapid and severe in onset, the medical confirmation of the determination of death by neurologic criteria should signal alert for a transition from failed neuro-resuscitation towards one of sustaining homeostasis and organ protection [94]. Validated paediatric recommendations, which are based on the main principles of adult treatment

[86-89], should be executed with precision while respecting good practices in EOL care [89, 93]. This timely medical decision of changing goal-directed therapies can be difficult for less experienced clinicians to identify [95]. It is vital to preserve the viability of organs following BD, which is pathophysiologically similar to sepsis with associated organ dysfunction [96].

Finally, the scarcity of available organs for transplantation requires that paediatric donors are promptly identified and provided with medical therapies to restore normal physiology and organ function that can maximise the number and quality of organs transplanted [20, 92]. Failures of identification or poor maintenance may be considered a failure of best medical practice.

Table 14.1. **Basic monitoring parameters**

Central body temperature
Invasive mean arterial pressure (MAP)
Heart rate
Urine output
Central venous pressure
Peripheral arterial oxygen saturation (SpO_2)
Arterial blood gas, pH
Arterial lactates (in each blood gas)
Na
K
Blood glucose
Calcium level
Haemoglobin
Platelets
Prothrombin time/partial thromboplastin time

14.7.1. Pathophysiological changes in paediatric brain death

Whatever the aetiology of the original severe brain injury that leads children to BD, the pathophysiological changes induced by an initial systemic pro-inflammatory response altering tissue homeostasis, followed by autonomic dysregulation in confirmed BD states, are deleterious for all organ function (see Chapter 5).

The autonomic dysregulation that occurs following BD is a consequence of the loss of central afferent nerves to the cardiovascular system, the respiratory, thermoregulatory centre, baro- and chemo-receptors and the hypothalamic-pituitary axis. Regardless of age, following BD the clinical appearance results in multifactorial haemodynamic instability similar to sepsis. Diabetes insipidus is frequently encountered following BD, besides hypothermia and decreased CO_2 production.

Osmotherapy, vasopressor and inotropic support instigated after the initial cerebral insult, co-existing cardiac co-morbidities and the previous haemodynamic state and medical treatment prior to BD can further aggravate circulatory instability in the potential donor.

Table 14.2. **Target parameters**

Haemodynamic support		
Normalisation of blood pressure		
Systolic blood pressure appropriate for age		
Lower systolic blood pressures may be acceptable if biomarkers such as lactate are normal		
Central venous pressure < 12 mmHg		
Dopamine < 10 µg/kg/min		
Normal serum lactate		
Blood pressure	**Systolic (mmHg)**	**Diastolic (mmHg)**
Neonate	60-90	35-60
Infant (6 mo)	80-95	50-65
Toddler (2 y)	85-100	50-65
School age (7 y)	90-115	60-70
Adolescent (15 y)	110-130	65-80
Fluids and electrolytes		
Serum Na+	130-150 mEq/L	
Serum K+	3-5.0 mEq/L	
Serum glucose	60-150 mg/dL	
Ionised Ca^{++}*	0.8-1.2 mmol/L	
Oxygenation and ventilation		
Maintain PaO_2 > 100 mmHg		
FiO_2 0.40		
Normalise $PaCO_2$ 35-45 mmHg		
Arterial pH 7.30-7.45		
Tidal volumes 8-10 mL/kg		
Positive end-expiratory pressure 5 cmH_2O		
Thermal regulation		
Core body temperature 36-38 °C		
Urinary output		
Maintain urinary output > 0.5-2.0 mL/kg/h		

*Calcium can improve blood pressure in neonates and infants.

Source: Modified with permission from Nakagawa TA, North American Transplant Coordinators (NATCO) Donor Management and Dosing Guidelines, available at www.organdonationalliance.org/toolbox/pediatric-donor-management-goals-and-dosing-guidelines/, accessed 14 July 2021.

The end result of all these altered mechanisms affecting vital parameters can jeopardise the organ function of potential donors. This requires the clinician to anticipate and initiate aggressive medical treatment throughout the period of donor support in the ICU until organ procurement can occur.

In the study by Tsai *et al.* one quarter of the po-

tential paediatric donors for whom parental consent was obtained were unable to complete the donation process due to pre-procurement instability during donor management prior to organ recovery [97].

14.7.2. Monitoring and target parameters

Circulatory disturbance in BD potential donors should be prioritised with invasive and non-invasive monitoring to ensure continued adequate organ perfusion and function. Regardless of age, basic monitoring should include pulse oximetry, core body temperature, invasive arterial and central venous pressures measurement and urinary output (Table 14.1). Serial echocardiograms can evaluate cardiac function and should be followed closely. For additional monitoring of thoracic organs function or in the case of haemodynamically unstable donors, advanced haemodynamic monitoring may include cardiac output/cardiac index, systemic vascular resistance and central venous oxygen saturation. Serial and trans-oesophageal echocardiography, invasive stroke volume index monitoring and pulmonary catheterisation can also be used (see Figure 14.3).

Donor management goals to preserve organs for transplantation should focus on normalising and maintaining haemodynamic stability, oxygenation and ventilation, and fluid and electrolyte balance, until organ procurement occurs (see Table 14.2).

14.7.3. General management of the paediatric organ donor

A strategy to maintain blood pressure and normovolaemia while optimising cardiac output, using the least amount of vasoactive agents, is promoted by many paediatric centres and DC/OPOs involved in organ recovery [86-89]. Although supporting evidence is lacking in both in adult and children (see Chapter 5), hormonal replacement therapy (HRT) is commonly used during initial management in North America to balance the use of inotropic agents and fluids during donor management to maintain the viability of organ function [86-89, 98].

14.7.3.1. *Hypovolaemia/hypotension*

The cessation of central autonomic stimulation with resulting vasodilation, along with the profound negative cardiovascular effects of pro-inflammatory agents and the dehydrating therapy to treat cerebral oedema, results in hypotension (absolute or relative) following BD. Management involves volume replacement (mean 59.5 mL/kg) to maintain haemodynamic status and end organ perfusion [92]. A balanced approach to volume replacement combined with vasoactive support should be used to preserve potential for lung recovery and transplantation.

14.7.3.1.1. Fluid management

Treatment of hypotension requires volume replacement using crystalloids or colloids to replace the intravascular fluid deficit. Synthetic volume expanders are not recommended for volume replacement in paediatrics [99]. Volumes of 20 to 60 mL/kg over the first hour may be required for the initial resuscitation and titrated to clinical markers of cardiac output that may also include the use of vasoactive agents to support blood pressure. Excessive volume replacement can lead to fluid overload affecting end organ function and should be closely monitored. After normalisation of the arterial pressure according to age, the solute content of replacement fluid is guided by serum sodium and glucose levels (e.g. glucose 2.5 % with added electrolytes). Intravascular volume status may be aided using central venous pressure (CVP 810 mmHg, and target urine output) with a goal to preserve euvolaemia and avoid overhydration which may lead to pulmonary oedema [86-89]. Importantly, urine output may not be reliable if diabetes insipidus is present.

14.7.3.1.2. Central diabetes insipidus

Although diabetes insipidus (DI) does not occur in all children following BD (though seen in 78 % of the cases in some reports) [92], it is frequently associated with profound fluid and electrolyte disturbances if present and not rapidly controlled (> 4 ml/kg/h). DI manifests with dilute urinary output (< 200 mOsm/kgH_2O) and hypernatraemia. Pharmacologic agents to control DI must be used in conjunction with volume replacement therapy to maintain a euvolaemic state and prevent hypovolaemia, haemodynamic instability, hypernatraemia (> 145 mmol/L) and hyper-osmolality (> 300 mOsm/kgH_2O) [98]. To maintain normal physiologic parameters, IV desmopressin administered continuously or by bolus or a continuous vasopressin infusion should be used to control urinary output and electrolyte balance as part of the care of the donor (see Table 14.3).

14.7.3.1.3. Other options

Mainly in US practice, initiating management with a vasopressin infusion, either alone or in conjunction with corticosteroid therapy and thyroid hormone replacement, may improve graft function and preserve donor stability prior to organ recovery [87, 100]. No published report indicates that HRT has deleterious effects in children, and exogenous supple-

mentation seems controversial in adults (for further information, see PICOS questions in Chapter 5, §5.5; see also appendices 7-8). Based on this premise, early initiation is not recommended until prospective confirmatory studies become available, but actually complete or partial HRT may be administered to unstable patients undergoing optimal haemodynamic care [20, 87, 101-102].

14.7.3.2. *Persistent hypotension*

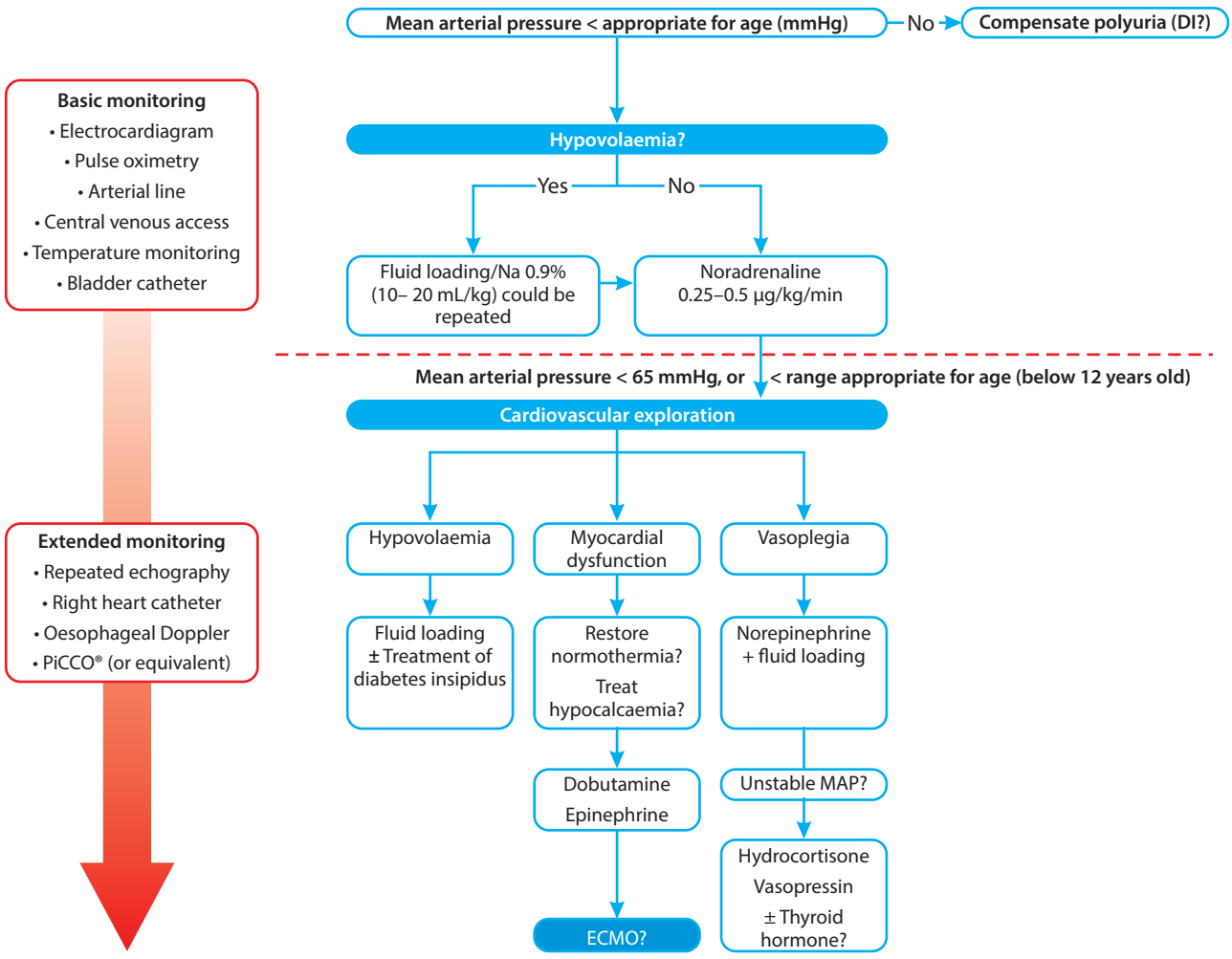
Figure 14.3 outlines the monitoring objectives used in the management of the potential paediatric organ donor after BD.

A target paediatric mean or systolic arterial pressure depending on age (Table 14.2) must be achieved and maintained, while targeting urine output between 0.5 and 2 mL/kg/h and using serum lactate as a marker of tissue perfusion. Restoring a normal blood pressure is achieved by volume administration with crystalloid/colloid solutions and use of vasoactive agents to treat hypotension and maintain a CVP of 4-12 mmHg (< 8 mmHg in potential lung donors) [103].

Administration of blood products as fresh frozen plasma or packed red blood cells can be used to treat hypotension in patients with a low haemoglobin level or coagulopathy.

If adequate arterial pressure for age or normalisation of serum lactate cannot be achieved by fluid replacement, vasopressors are justified. In case of persistent instability, the use of HRT may be considered to help establish normal physiologic parameters in BD donor [87, 89].

Figure 14.3. **Haemodynamic objectives and care in the management of the paediatric potential organ donor after brain death**



DI: Diabetes insipidus; MAP: Mean arterial pressure; PICCO®: Minimally invasive cardiac output; ECMO: Extracorporeal membrane oxygenation.

Source: modified from Charpentier J, Cariou A. Objectifs et moyens de la prise en charge hémo-dynamique. In: G Boulard, P Guiot, T Pottecher, A Tenaillon, *eds. Prise en charge des sujets en état de mort encéphalique dans l'optique du prélèvement d'organes et de tissus*. Paris: Elsevier, 2005:125-35 [103].

14.7.3.2.1. Vasopressors

Sustained hypotension has been described in half of paediatric donors [92]. After replacing fluid volume, use of vasopressor support should be determined by the patient's haemodynamic profile. If multi-organ dysfunction is present, extended haemodynamic monitoring such as serial echocardiography, minimally invasive cardiac output (PICCO® or equivalent) and, rarely, pulmonary catheterisation should be applied [103].

Dopamine has traditionally and consistently been considered as the first-line vasoactive agent in paediatric septic shock [99] and donor management practices in US [89, 104] (Figure 14.3). The international guidelines for the management of sepsis in children were unable to issue a recommendation for a first-line vasoactive agent therapy in septic shock but suggested using norepinephrine or epinephrine rather than dopamine [102]. Norepinephrine is commonly used without report of serious complications from vasoconstriction. A maintenance dose from 0.2 to 0.5 µg/kg/min to maintain the targeted arterial pressure is recommended.

Adult and paediatric studies show that low-dose dopamine has decreased the risk of organ vessel dilatation or dysfunction in donor management [105-106], and has no short- or long-term effect on graft function [107]. However, higher-dose dopamine (> 10 µg/kg/min) and epinephrine or norepinephrine in excessive doses all exhibit alpha-agonist activation, leading to potential excessive vasoconstriction that can compromise organ perfusion [86-87, 108].

Vasopressin is commonly used in hormonal replacement therapy for DI in the treatment of the paediatric organ donor. The vasoconstrictive effect of vasopressin can augment blood pressure. In a retrospective study, a low dose of vasopressin administered in continuous infusion (0.04 units/kg/h ± 0.069) improved haemodynamic parameters without deterioration in organ function and decreased the infusion rates of other catecholamines, mainly epinephrine and dobutamine [109].

14.7.3.2.2. Myocardial dysfunction

The autonomic storm observed during the agonal phase of brain herniation is the common underlying pathophysiologic pathway to systolic or diastolic myocardial dysfunction following BD. Myocardial dysfunction occurs in a high percentage of donors who progress to BD and has been reported in 10 to 40 % of adult donors [110] and 40 to 57 % of paediatric donors [111-112]. The majority of paediatric donors (73 %) show improved cardiac function over time, allowing for potential organ recovery for transplantation [113].

Myocardial dysfunction is easily assessed and quantified by Doppler echocardiography. Serial transthoracic echocardiograms in patients with cardiac dysfunction show improvement of cardiac function in most patients, suggesting that initial decisions to procure the heart should not depend solely on the initial transthoracic echocardiogram examination results [113-114]. In the absence of randomised controlled trials studying optimised catecholamine regimen in such situations, inotropic support should be recommended [20], as epinephrine (or dobutamine) for septic cases [102], in association with judicious use of norepinephrine and fluids [103] to optimise total haemodynamic status and maximise the chance of successful transplantations (Figure 14.3).

Deleterious cardiac effect of the autonomic storm including tachycardia and myocardial oxygen consumption may be mitigated, at least in adults, by a beta-adrenergic antagonist such as Esmolol [115-116].

14.7.3.3. *Endocrine considerations*

Several pathways involving neuro-hormonal signalling are responsible for maintaining haemodynamic, metabolic and inflammatory/immunologic homeostasis. Loss of hypothalamic and pituitary function following BD induces endocrine dysregulation that contributes to end organ damage. Following BD, loss of arginine vasopressin due to posterior pituitary dysfunction is a common finding, in addition to thyroid hormone and cortisol, which are more variably affected. The alteration of endocrine function could be supplemented with exogenous HRT (Table 14.3). However, HRT for neuroendocrine alterations following BD continues to be regarded as controversial by some clinicians because of conflicting evidence in adults and the absence of specific studies in paediatric donor management (see the PICOS Questions in Chapter 5; see also Appendix 8).

14.7.3.3.1. Arginine vasopressin

Arginine vasopressin (AVP) has a dual effect that promotes 'vasoconstriction' and 'reabsorption of water' in the renal collecting tubules. The Organ Procurement and Transplantation Network Registry evaluated the use of AVP and HRT on more than 10 431 BD donors. HRT was independently associated with an increased rate of adult organ recovery [100]. Review of HRT used in 1 903 paediatric donors complied from the United Network of Organ Sharing in the US showed that HRT was associated with signifi-

cantly increased odds of having the liver and at least one kidney and lung transplanted [117].

Table 14.3. **Agents for paediatric hormonal replacement: suggested dosing**

Hormone and indication	Dosing range			Comments
Arginine vasopressin (AVP) for diabetes insipidus	0.0002-0.01 IU/kg/h			Titrate to urine output 0.5-3.0 mL/kg/h and serum sodium 130-155 mmol/L
Desmopressin (DDAVP) for diabetes insipidus	0.25-1 µg IV every 6h			
Arginine vasopressin (AVP) for vasodilatory shock	0.0003-0.0025 units/kg/min infusion			Titrate to normal blood pressure for age and markers of cardiac output
Methylprednisolone for immunosuppression	15-30 mg/kg IV once daily (suggested maximum dose 1 000 mg)			Collect immunotyping samples before administration
Insulin for hyperglycaemia	0.02-0.1 IU/kg/h infusion			Monitor for hypoglycaemia; consider avoiding use in pancreas procurement
Thyroxine (T4) for hypothyroidism	***Age***	***Load (µg/kg)***	***Infusion (µg/kg/h)***	Consider use with refractory hypotension and/or cardiac dysfunction
	0-6 mo	5	1.4	
	6-12 mo	4	1.3	
	1-5 y	3	1.2	
	6-12 y	2.5	1.0	
	12-16 y	1.5	0.8	
	> 16 y	0.8	0.8	
Combined hormonal therapy • AVP/desmopressin • Thyroxine (T4) • Methylprednisolone • (± Insulin)	As above			Routine use in paediatric organ donors eligible for heart, lung and/or kidney procurement, as well as those demonstrating cardiac dysfunction

Source: Gupta and Dhanani, Endocrine considerations of the pediatric organ donor. *J Pediatr Intensive Care* 2016;5:205-12 [98].

The frequency of DI in children following BD is 40 % [118] to 78 % [92]. Untreated, DI will result in severely impaired organ function of potentially transplantable organs. Haemodynamic instability occurs from diuresis-induced hypovolaemia. Hypernatraemia from hyper-osmolality-induced intracellular fluid imbalance follows. Correction of hypovolaemia and hypernatraemia is imperative to preserve organ function in any donor. Hypernatraemia can affect organs for transplantation, especially the liver. Two retrospective paediatric studies reporting on the complications related to donor livers did not find an association with poor graft function and hypernatraemia [119-120]. Paediatric organ donors with DI may be managed with intravenous desmopressin (DDAVP) every 6 or 12 hours (see Table 14.3) or by continuous infusion. Treatment with AVP or desmopressin in conjunction with use of hypotonic solutions for urine replacement or enteral free water may assist with normalising serum Na concentrations [87]. Donor management goals recommend maintaining serum Na concentration at less than 155-160 mmol/L. Infusion of AVP in higher doses is used in critically ill children with vasodilatory shock [121]. Katz *et al.* retrospectively demonstrated that low-dose AVP had a vasopressor sparing effect in the critically unstable BD donor, with low risk of splanchnic vasoconstriction and organ toxicity [109].

14.7.3.3.2. Thyroid hormone

Thyroid hormone depletion results in impaired cellular respiration and causes a shift to anaerobic metabolism with lactate accumulation [98]. Although the use of thyroid hormone in BD children has been shown to decrease the need for inotropic support in this population [122] (Table 14.3), the most recent update to Canadian recommendations did not recommend this practice, except in haemodynamically unstable patients, as is already accepted practice by the majority of European and US guidelines for BD donors [108] (see the PICOS Questions in Chapter 5; see also Appendix 8).

14.7.3.3.3. Steroids

Cortisol release from adrenal glands is induced by the adrenocorticotropic hormone (ACTH), which is produced by the anterior part of the pituitary gland. In BD patients, steroid replacement for adrenal insufficiency and modulation of inflammatory cascades

by the regulation of the donor's immune response to brain peptides [96] are the most relevant roles of cortisol administration (Table 14.3). Additionally, corticosteroid administration upregulates beta receptors and can reduce lung free water in the donor [87, 89]. Although there is no evidence that reduced cortisol levels in potential adult or paediatric donors are associated with poorer transplant outcomes [98], therapeutic administration should be considered in cases of pre-existing or clinically suspected adrenal insufficiency. A systematic review by Dupuis *et al.* in 11 randomised studies shows that there is no evidence to support steroid administration, whereas results seen in 14 observational studies indicated that steroids may be associated with an improved transplant recipient outcome [123]. Currently, it is recommended that methylprednisolone may be useful in unstable potential donors unresponsive to optimal haemodynamic care, as a rescue therapy with vasopressin and thyroid hormone (see PICOS Questions in Chapter 5, §5.4.1; see also Appendix 7).

14.7.3.3.4. Insulin

Hyperglycaemia (glucose > 180 mg/dL) has been reported in 48 % of paediatric donors aged under 5 years and 28 % of donors between 5 and 12 years [124]. Many factors contribute to hyperoglycaemia in the donor, including endogenous or exogenous catecholamine circulation, corticosteroid administration, glucose infusions, catecholamine-induced insulin resistance and decreased metabolism following BD, and it may be associated with reduced renal function in deceased donor [98].

14.7.3.3.5. Hormonal replacement therapy

United States organ donor guidelines suggest that early initiation of HRT may be beneficial and should be strongly considered for paediatric donor management. However, the benefits of corticosteroid and thyroid hormones remain untested prospectively in the paediatric donor, and there is only limited evidence to show a benefit of AVP on haemodynamic status in children. Importantly, no published report indicates that HRT has deleterious effects in children [87]. Pharmacologic agents for HRT (outlined in Table 14.3) are recommended mainly for management of haemodynamically unstable donors despite optimal haemodynamic care, with the aim of restoring normal metabolic parameters. (For more information, see Chapter 5.)

14.7.3.4. *Hypothermia and dysregulation*

Thermoregulatory mechanisms cease after BD while heat loss continues via convection and radiation. Hypothermia also occurs because of profound vasodilation with heat loss and infusions of unwarmed intravenous fluids and blood products. Hypothermia can contribute to severe systemic complications such as direct myocardial depression increasing hypotension, cold diuresis, coagulopathy and potentially decreased oxygen delivery to the tissues by shifting the haemoglobin oxygen dissociation curve [125]. In all cases, the patient's temperature should be maintained above 35 °C to preserve organ function and limit complications associated with hypothermia.

14.7.3.5. *Protective respiratory considerations*

The limited number of paediatric donors drastically affects recovery of lungs for transplantation. Every donor should be managed as a potential lung donor. Recovery and transplantation of lungs from a BD donor remains one of the most challenging aspects of donor management. Lungs are susceptible to damage by a number of factors including traumatic contusions to the lung or airway injury, resuscitation manoeuvres, pneumonia, neurogenic pulmonary oedema, SIRS, excessive volume resuscitation and suboptimal ventilation support. A chest CT scan may be useful to delineate pulmonary anatomy and pathology, guide intensive care staff in donor management and determine suitability for transplantation.

A protective lung ventilation strategy using the lowest possible plateau pressure and moderate positive end expiratory pressure (PEEP) to achieve oxygen saturation of > 92 % and arterial pH 7.35-7.45, is strongly recommended [20, 108, 126]. In a multicentre randomised controlled trial involving 118 potential adult donors, a protective ventilation strategy using tidal volumes of 6 mL/kg ideal body weight, PEEP > 8-10 cmH_2O and alveolar recruitment manoeuvres was found to double lung transplant rates from 27 to 54 % [127]. The paediatric literature lacks significant evidence about pulmonary management of the BD donor. Best practices highlighted through the US Organ Transplant Breakthrough Collaborative have demonstrated that up to 50 % of potential donors can yield lungs for transplantation, depending on size and age of the donor [126]. There is universal agreement in recognising the practice of airway protection using a cuffed endotracheal tube and the importance of alveolar recruitment manoeuvres to prevent respiratory deterioration. This includes ventilator management and regular repositioning and suctioning, with a goal of obtaining a PaO_2/FiO_2 ratio > 300 and a normal chest radiograph.

Invasive haemodynamic monitoring – including a central venous catheter to measure CVP – may assist with pulmonary management and help

reduce neurogenic pulmonary or pulmonary oedema from excessive fluid administration or replacement.

Pneumonia is determined by changes identified in the chest radiograph, tracheal or bronchial cultures, deteriorating in oxygenation and ventilation, and inflammatory markers in the blood stream. Pneumonia must be promptly diagnosed and aggressively treated. Treatment should be guided by culture results and the antibiotic susceptibility of the organism.

14.7.3.6. *Spinal movements*

Massive reflex or spontaneous automatic movements (usually without simultaneous EEG signal) may be observed, sometimes associated with hypertension and/or tachycardia. During organ procurement, administration of opioid drugs and neuromuscular relaxing agents may be advisable to avoid spinal reflexes and hypertension caused by surgical stimulation and to reduce bleeding [128].

14.7.3.7. *Nutritional support*

Enteral nutrition is recommended by some transplant teams to preserve the villous mucosa of the small bowel if it is being transplanted [87]. Collaboration with the DC/OPO and the transplant team is recommended when considering enteral nutrition in the donor.

14.7.3.8. *Haemostasis and procurement*

Haematological parameters should be monitored and maintained in the normal range for the paediatric donor. Specific considerations include:

a. Maintain a sufficient haemoglobin concentration adapted to age and haemodynamic status to preserve oxygen delivery to organs. Over 1 year, no recommendations exist to transfuse critically ill children, or those at risk of critical illness, who are haemodynamically stable with haemoglobin concentration > 7 g/dL. Under 1 year, a haemoglobin concentration > 9 g/dL may be considered [129].

b. Excessive transfusion of blood and blood products can result in difficulty completing pre-procurement serological tests because of possible dilution effects. Early blood sampling prior to transfusion may avoid this challenge.

c. Coagulopathy during the management process or prior to organ recovery requires correction of clotting factors and platelet levels ($> 50 \times 10^9$/L) [87].

14.7.3.9. *Infectious disease considerations*

Patients with systemic bacterial infections may still be suitable for organ donation. Adequate treatment of the bacterial infection can result in organs that are viable for transplantation [20]. Since in mild or asymptomatic donors infectious transmission remains a possibility, potential donor-to-recipient infectious transmission must be anticipated, and a thorough routine screening of donors is mandated before organ recovery and transplantation [130] (for more information see Chapter 8).

Previous reports have indicated that paediatric donors are much more likely to transmit viral infection (46 %) than adult donors (19 %) [131]. Infections in general were by far the primary transmission event type from paediatric donors to recipients [131]. Donor history is typically well known by parents of small children but may be largely unknown in teenagers or adolescent patients where social activities may not have been disclosed to parents by the child. The risk of transmission of an infectious disease that can be treated to a potential transplant recipient who will be immunosuppressed should be balanced with the risk of declining a rare organ donor with an opportunity that might be life-saving. Final decisions on specific donors and circumstances regarding organ recovery are often made on a case-by-case basis. This requires routine collaboration between transplant teams, infectious disease specialists, immunologic experts and the DC/OPO [132].

14.7.3.10. *Extracorporeal membranous oxygenation (ECMO)*

Brain dead donors with ongoing ECMO and continuous renal replacement therapy may preserve circulatory stability and correct fluid and electrolyte disturbances, and then increase organ donation success.

On the other hand, once the BD diagnosis has been pronounced and consent for organ donation obtained, in persistently unstable patients requiring ongoing cardiovascular support or resuscitation, ECMO has been used as a bridge to stabilise organ perfusion until organ procurement can occur [133].

14.7.3.11. *Optimising management in cases of paediatric brain death*

14.7.3.11.1. Optimising timely management

Organ donation is a part of EOL care. Families facing EOL issues for their child in the ICU should be offered the opportunity of organ donation. Optimal patient management is also ethically sound and should be maintained until a determination of death

has occurred or decisions about ongoing medical treatment have been established with the family. The continuum of care must preserve the option of organ donation. This process requires collaboration between all professionals in the ICU. Early identification of a possible organ donor, with notification of the donation staff, is considered best practice to increase organ donation [20]. Ongoing patient management and progression to BD should be determined by a skilled intensive care specialist [134-136].

Determination of BD should be made in a timely manner, and information should be conveyed to the family so that decisions about donation and other EOL issues can be discussed. Ongoing support for the patient who becomes a donor allows for high-quality organ management to enhance organ recovery for transplantation. The intensive care specialist plays a key role in the donation process with interaction and co-ordination between ICU, donor co-ordinator or OPO staff, and the organ procurement team [20, 137].

14.7.3.11.2. Optimising the paediatric donor management until procurement

Little evidence-based research has been published on protocols or specific management practices for paediatric organ donors. Following the consensus statement by the Society of Critical Care Medicine by Kotloff *et al.* in 2015 [87], all 58 OPOs in the US participated in Robert Ream's evaluation study on the use of guidelines and routine practices for the management of paediatric organ donors [104]. Study conclusions revealed that all OPOs used various forms of HRT. The majority employed written paediatric donor management guidelines for haemodynamic, thermoregulation, fluids and electrolyte correction, but wide variations were observed in glycaemic control and pulmonary management using mechanical ventilation [104].

Homeostatic disruptions affecting all organ systems are commonly seen in paediatric donors. While these disruptions may vary in each donor, hypotension and DI are commonly observed followed by anaemia and hyperglycaemia [124]. Homeostatic disorders can develop at any time after the onset of ischaemic brain injury that progresses to BD. Close monitoring for haemodynamic, respiratory, fluid and electrolyte, and thermoregulatory alterations justifies the need for intensive monitoring to recognise and correct these alterations during the process from BD to the parental authorisation for donation and organ procurement.

In 1997, Finfer *et al.* [92] described better allograft function when hypovolaemia and hypernatraemia associated with DI were recognised early and treated, emphasising the need for early and attentive management of the donor to restore normal physiologic parameters following BD. As a result of early donor management and use of donor management protocols, 93 paediatric heart transplants in 2005 demonstrated improved rejection-free survival in heart recipients with longer periods between confirmation of BD and organ recovery [138].

Best paediatric donation practice includes preserving the option of donation for all potential eligible donors prior to and following declaration of death [20, 86-87]. The continuum of care from admission through the dying process and recovery of organs requires a skilled group of paediatric providers to manage the numerous physiologic alterations that occur during the process of BD.

14.8. Paediatric donation after the circulatory determination of death

Whether due to the course of a chronic illness or following an unanticipated accident, the emotional impact of the death of a child affects both the family and the professional caregivers of the child. Caregivers must discuss EOL issues, including organ donation, with families and surrogate decision makers during a difficult time when grief and loss consume the emotional aspects for all involved. In pDCD, providers may feel the added pressure of integrating donation into EOL care because this process alters some aspects of routine WLST. For these and other reasons, pDCD remains an uncommon event in most countries [15]. Successfully performing pDCD requires careful planning and a system dedicated to offering donation to all potentially eligible donors. Some European countries have developed such a system (UK, the Netherlands and Spain), but many others have not – the reasons for this are at least partly found in the pronounced variability in EOL practices throughout Europe, which we consider later in the ethical issues section (§14.8.3) [139].

pDCD shares many similarities with adult DCD, with the significant exception that all reported pDCD is from the controlled pathway (Maastricht III donors). To our knowledge, no jurisdiction has an active uncontrolled pDCD program (Maastricht II). Thus, almost all pDCD donation occurs after WLST, usually mechanical ventilation. An overview of a typical controlled pDCD, which is similar to that for adults, is provided in Chapter 12. As in any controlled DCD process, surrogate decision makers must have

finalised the consensual decision to pursue WLST prior to discussion of organ donation potential. There are instances where a BD donor is converted to a DCD donor because of instability or family requests to be with their child until the heart stops beating.

This section will focus on the practice of pDCD, including factors that contribute to the relatively low rates of pDCD activity globally, application of pDCD to specific paediatric populations such as neonates or infants born with anencephaly, and ethical issues specific to the paediatric population.

14.8.1. Epidemiology and outcomes

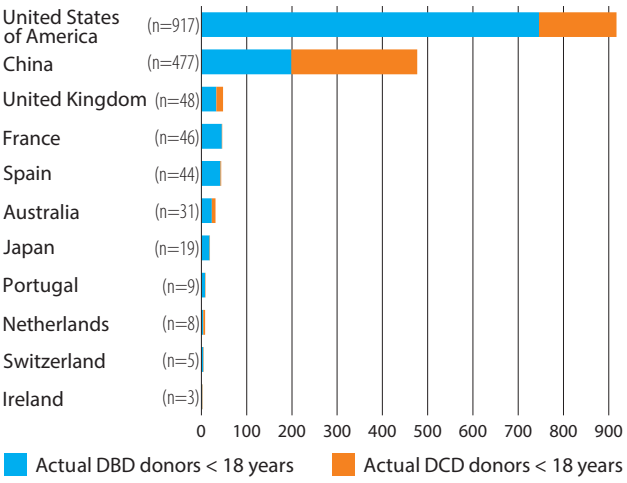
Compared to adult DCD, pDCD is an infrequent event, though details of the epidemiology of this practice in most countries are poorly understood [11]. Countries use different criteria when defining a paediatric patient (e.g., age up to 15 *v.* 18 years) and reporting of paediatric donation activity is not routine or standard in many countries. Despite these limitations, some generalisations can be made from the few countries that have reported detailed data [21].

Figure 14.4 shows the absolute number of actual deceased donors < 18 years of age (pDBD and pDCD pathways included) and the proportion of pDCD activity relative to overall paediatric deceased donation in countries with pDCD activity that was reported to the Global Observatory in 2019. As expected, the variability between countries is also reflected in their relative performance of controlled DCD in the adult population. For instance, in Spain controlled DCD was only piloted in the adult population in 2009, and pDCD was not practised until 2012 [4, 140]. This is in contrast to the UK, US and Australia where controlled DCD is well established in the adult and paediatric populations [5, 7-8]. These data suggest that a key factor to success in pDCD is development of a robust adult controlled DCD system. Indeed, in several European countries with active DCD programmes, pDCD, while lawful, is still not practised.

Even in countries with active pDCD programmes, it is a rare event. In the US in 2020 there were 176 pDCD actual donors under 18 years, or 0.55 per million population (pmp). In the same year there were 3 048 adult DCD donors or 9.5 pmp [5]. The possible reasons for this are multifactorial, and include age restrictions, uncertainty about eligibility criteria, low approach rates of families and surrogate decision makers, and lower mortality rates of paediatric patients [92]. Current DCD statistics from the US show continued growth and reveal that pDCD donors account for 8-9 % of the DCD donor pool [5].

The outcome of organs transplanted from pDCD donors is limited mainly to single-centre series or a few database reports. As summarised in a 2016 scoping review on the topic, organs from pDCD donors generally have outcomes that are comparable to organs from pDBD donors, with the exception of increased biliary complications in some hepatic transplant recipients [41]. The lower size limits of eligible pDCD donors is currently unknown; some centres have reported successfully recovering and transplanting *en bloc* kidneys from neonates as small as 1.9 kg [141]. Lack of knowledge about long-term outcomes is likely to be a contributing factor to reluctance by many programmes to consider smaller children as potential DCD donors.

Figure 14.4. **Absolute numbers of actual paediatric donors (total, pDBD and pDCD), 2019**



Source: Global Observatory on Organ Donation and Transplantation, data provided upon direct request, www.transplant-observatory.org/ [3].

Data include all paediatric deceased donors in 2019 in countries with pDCD activity reported to the Global Observatory. pDBD: Donors after brain death, age < 18. pDCD: Donors after circulatory determination of death, age < 18.

14.8.2. Death determination

The determination of human death must be safe and reliable. Two methods commonly used in most countries are neurological and circulatory determination of death. The former has been previously described (see Chapter 3 and, specifically for the paediatric population, §14.6). Determination of BD varies between countries and within countries and jurisdictions, depending on age and even the religious beliefs of the patient or family [70-71]. No such variability exists with the circulatory determination of death, which occurs in every country and with little practical difference in process (for more information see Chapter 12) with the exception of the ob-

servation or no-touch period to determine if return of spontaneous circulation will occur.

The majority of human deaths are verified by the lack of endogenous cardiorespiratory function, sometimes with certain neurological components. Circulatory death relies on a practical bedside test without need for confirmatory complex investigations, and with minimal preconditions – most notably the absence of profound hypothermia. In a non-donation setting, the absence of a palpable pulse and of spontaneous respiratory effort, together with the absence of any response to deep stimuli and fixed dilated pupils, form the bedside practical assessment to determine circulatory death. Without the possibility of donation, there is usually little urgency for verification to occur, though a reasonable time period since attempts at resuscitation is recommended. While there have been descriptions of spontaneous return of circulation after long periods of time, no such verified return has recurred after 5 minutes in the absence of attempted resuscitation [142-143]. No paediatric cases have been reported after WLST when no CPR manoeuvres were performed. Spontaneous return of circulation has been observed in 3 children, two minutes after the cessation of unsuccessful CPR [143].

Determination of death by circulatory criteria must be performed by predefined, objective criteria. Though some centres may still use palpable pulse to determine arrest of circulation, there are concerns from the resuscitation literature that palpable pulse may not be accurate in low-flow states [144]. Most recommendations suggest more objective criteria be employed, preferably an indwelling arterial line, but electrocardiogram, echocardiography or arterial Doppler are also acceptable [24-25]. Importantly, circulatory death is the loss of pulse pressure, not electrical activity (for more information see Chapter 12).

The need for well-defined methods and time limits for death determination is particularly important in pDCD as theoretically the younger myocardium may be resistant to hypoxic-ischaemic injury. However, there are no validated reports of autoresuscitation even in paediatric patients past five minutes of observation, and that is likely more important in maintaining public confidence in the clinicians' ability to verify death safely as a crucial part of deceased donor transplantation [143].

14.8.3. Ethical issues

With the resurgence of DCD, the need to safely verify death in a more rapid time frame is balanced with the need to reduce warm ischaemic damage to potentially transplantable organs. Ethical concerns about deceased donor transplantation have led to fundamental considerations about definitions of life and death [145]. In pDCD, some clinicians raised serious concerns about whether donors were really dead, although many of the concerns raised find their debates in the philosophical arena rather than the clinical realm [146].

The practical aspect of this deliberation was manifested by the reduction in the time after circulatory arrest when death could be verified safely. For some, the 10 minutes recommended by the Institute of Medicine in all patients, largely based on adult data, meant unnecessary warm ischaemic time to organs in the donor, and reductions in the time period followed [147-148]. For others, even 10 minutes was unsafe, and DCD should never be permitted [147]. One group of clinicians reduced the time as to as little as 75 seconds in infants to perform the first contemporary DCD heart transplants under an approved Institutional Review Board study [49]. This

Table 14.4. **Analysis of *ante mortem* interventions in dying children to optimise organ donation**

Interventions	Process	Equivalent use
Delayed WLST	Enable donation	Visitors to attend +/– religious observation
Transfer to theatre	Minimise warm ischaemia	For a surgical intervention
Heparin use	Prevent clots in organs	Anti-coagulation for DVT
Arterial line	Death verification	Haemodynamic monitoring
Bronchoscopy	Assess lungs pre- & post-transplant	Toilet airways
Blood tests	Matching, infection screen	Ongoing monitoring
Inotropes/fluids	Maintain organ viability	LST
ECMO	Potential for organ stabilisation	LST
Biopsy	Ensure safety of transplant	Diagnosis

DVT: Deep venous thrombosis. LST: Life-sustaining therapy. ECMO: Extracorporeal membrane oxygenation.

From: Brierley J, Shaw D. Premortem interventions in dying children to optimise organ donation: an ethical analysis. *J Med Ethics* 2016; 42(7):424-8 [151].

study proved controversial, with calls for a moratorium on DCD [147]. No other centres have adopted such a short 'stand-off period' of less than 2 minutes and the international consensus is that 5 minutes is a safe and reasonable time period, though other countries have maintained 10 minutes [68]. The safety of this approach has been supported by both prospective and retrospective research in paediatric and adult patients that has shown in the setting of elective cessation of life-sustaining therapy and the absence of recent cardiopulmonary resuscitation, there is no spontaneous return of circulation (autoresuscitation) – the Lazarus phenomenon [149]. Additionally, DCD has been extensively reviewed by medical organisations that have found no ethical issues related to this type of donation if performed within specific guidelines [26-27, 150].

There are a number of ethical considerations in pDCD, although some are actually more accurately described as psychological concerns involving the emotiveness of the death of a child. Indeed, variability throughout Europe in the permissibility or practice of DCD is more linked to national standards related to WLST in children rather than donation practices. Examples include: DCD is unlawful in Germany; pDCD is not currently practised in Switzerland and France, despite adult DCD occurring; pDCD is practised in the Netherlands, UK and Spain.

Outside this variability, where pDCD is offered, the key ethical issues involve: the decision on WLST, the ability of parents/the child to give valid consent/authorisation to the process of DCD, the safe and reliable verification of death discussed above, and interventions used to improve organ performance for transplantation.

a. Traditionally, the decision on WLST must be made before any consideration of donation. This ensures no undue influence or conflict of interest on the process of determining the best interest of the (potentially) dying child. This does not necessarily mean that discussing donation is unethical before the actual donation discussion itself happens – a stance supported by bereaved and non-bereaved parents [137]. If the parents raise the topic, however, organ donation may be addressed during conversations leading to a WLST decision.

b. In pDCD those patients/parents/guardians able to provide consent/authorisation, including WLST, must be able to do so with full information about the process. This is clearly different from an adult donor who has the ability to opt out, or opt in, depending on jurisdiction.

c. The final major ethical consideration we identify is those interventions carried out in the donor to improve the quality of recovered organs that may be used during the process of DCD (Table 14.4) [151]. Unlike BD, DCD is considered in a living child afforded all the protections under law. As not all potential candidates for DCD will die following WLST, the level of intervention permissible to aid in organ viability must be primarily considered on a harm calculation, with no medical benefit to the donor, but taking into consideration the honouring of the child's and family's legacy with the objective of creating the best donation and EOL care possible. The risk of harm that the potential donor might tolerate should not be different from the risk that any child in the PICU will accept for curative purposes. Reasons for this are: the potential donor will not directly benefit from these interventions, and the likelihood of becoming an organ donor are uncertain. Many interventions are standard for children admitted to the PICU, and therefore may be more readily acceptable as they carry minimal or mitigatable chance of harm and are designed to help the child [151].

Another important issue is that there can be no decreased quality of expert EOL supportive care to a potential pDCD donor and their family. There is actually evidence from adult practice that EOL care is improved by DCD considerations.

Perhaps the biggest ethical issues in pDCD are the failure of healthcare teams to refer children for donation considered as part of holistic child-centred EOL care, the failure of national governments to recognise the importance of saving lives of their citizens and the provision of support mechanisms in our societies – whether cultural, spiritual or practical – to help bereaved parents save the lives of other children [21]. Educational efforts and training focus for paediatricians' needs must be advanced, so that they feel confident about maintaining conversations on organ donation with the grieving parents and understand the important role of the DC.

14.8.4. Special considerations

Organ donation from infants with anencephaly after BD is no longer internationally acceptable due to the ethical and practical complexity of determining death by neurologic criteria [152]. However, pDCD is possible, but requires either a transplant team present at delivery, which is rarely achievable, or elective institution of life-sustaining therapy for

donation purposes such as intubation and respiratory support, which brings its own ethical challenges [27, 153]. Successful recovery of organs for transplantation after pDCD from anencephalic infants has occurred but is rarely reported [154].

Despite initial ethical reservations surrounding the verification of cardiorespiratory death in DCD, most accept death as a uniform entity, which means allowing most organs – including lungs, liver, kidneys, pancreas and intestine – to be procured after declaration of death. pDCD cardiac transplantation without the use of external circulatory support has been reported in the US [49] but has not expanded outside the original centre due to technical and ethical limitations. More recently, successful adult cardiac DCD has been reported internationally, with occasional teenage cases using *ex situ* perfusion strategies [155]. We await *ex situ* support systems that can be used to support organs from smaller children, allowing benefit from this life-saving intervention to children.

The use of normothermic regional perfusion (NRP), based on the use of ECMO devices, has potential advantages in terms of the number and quality of organs obtained from controlled DCD donors (see Chapter 11 and Chapter 12). NRP allows the *in situ* preservation of organs with oxygenated blood after the determination of death and prior to organ recovery. Measures need to be implemented to restrict preservation to organs subject to transplantation (abdominal and thoracic organs) and to avoid reperfusion of the brain, which would retroactively negate the previous diagnosis of death by circulatory criteria. Reliable isolation of the cerebral vascular supply is less secure in children than in adults, due to greater collateral circulation, meaning this cannot be recommended without greater safety data. Manara *et al.* have described some refinements to current protocols that can help to monitor and exclude brain reperfusion during *in situ* NRP [156].

14.8.5. Knowledge and practice gaps

Consistent with all forms of donation, a major obstacle for pDCD is identification of patients who are potential donors and referral to the procurement specialists. Few countries have effective, national audits of potential donors, so the rates of identification and referral are not always evident when making comparisons between or even within countries or jurisdictions. Existing paediatric-specific data suggest that there is substantial opportunity for improvement. A 2018 report from the UK found that only 40 % of paediatric patients who meet referral criteria for organ donation were actually referred, and only 33 % of families of potentially eligible children were approached [93]. Without systematic potential donor audit practices to ensure that all patients who are potential donors, including pDCD, are identified and their surrogate decision makers or families approached, donation opportunities will continue to be missed.

Other areas for improvement in donation practices include standardising eligibility criteria, inexperience of transplant programmes in the use of small pDCD organs and compliance with accepted best practice to ensure that pDCD is a routinely offered aspect of EOL care. Some efforts have been made, including paediatric-specific national guidelines and the integration of paediatric-specific recommendations in other countries' global DCD efforts [12, 24]. Creating and sharing best practice internationally was an expressed goal of a recent paediatric-focused donation meeting [10]. These guidelines, however, will be limited as long as the state of understanding of some foundational aspects of pDCD remain poorly understood. Researchers and policy makers in the field have identified a pressing need to fill knowledge gaps that include a better understanding of outcomes of pDCD recovered organs, the physiology of the dying practice for paediatric patients after WLST, the effects of functional and absolute warm ischaemic time on pDCD organs, the application of *in situ* and *ex situ* organ support technology (including hearts) and the best methods to ensure that all patients who are potential donors are referred for donation consideration.

Adult DCD has greatly expanded the number of life-saving organ transplantations and provides the chance for family members to honour a desire of their loved one to donate organs after death. By improving and standardising pDCD practices, the full potential of this option can also be offered to families of children at the end of their lives [157].

14.9. Organ procurement and transplantation in infants and children

Although there is a lot of literature regarding the management of paediatric organ donors at ICU (clinical, pharmacological and psychosocial aspects) [10, 33, 101, 111, 118, 124, 137], almost nothing has been published up to now about the technical aspects of organ procurement operations in paediatric donors [158].

In this section we report on peculiarities of

organ procurement in paediatric donors that may influence the outcome of the transplant. In the second part we briefly report on organ procurement techniques and the long-term results of paediatric organ transplantation.

14.9.1. General aspects of organ procurement in paediatric deceased donors

The general rules and technical principles of organ procurement in adult deceased organ donors [159] can be also applied in the context of paediatric organ donors. Special attention should be given to the following unique aspects related to donation in children:

a. Small size of vessels and organs commonly encountered in children and in particular small babies < 1 year of age. The organ recovery surgeon must be familiar with paediatric surgery and paediatric transplantation, and the use of magnification glasses during the procurement operation is strongly recommended. Surgeons with expertise in paediatric patients must lead the procurement for optimisation of the organs. Damage during recovery can result in a non-transplantable organ.

b. Vascular anatomy: the procurement surgeon should keep in mind that in children the distance between coeliac trunk, superior mesenteric artery and renal arteries is very small (i.e. < 5 mm). This aspect must be considered in case there is need for an aortic patch for each organ supplied by the above-mentioned vessels (i.e. liver, kidney, intestine).

c. Systemic donor heparinisation before cross-clamping using a suggested dose of 300 IU heparin/kg body weight.

d. Cannulation of distal abdominal aorta for *in situ* organ perfusion: the cannulation of the distal abdominal aorta directly above its bifurcation into the iliac vessels is suggested. In children the diameter of the aorta itself is usually < 10 mm and often < 5 mm. Special smaller cannulas should be available for cannulation prior to perfusion. Cannulation of the small iliac vessels should be avoided, and it can compromise the available length of the iliac vessels that may be needed for vascular reconstruction or elongation. The superior and inferior mesenteric arteries should be kept intact and not be ligated and divided as proposed by Muiesan *et al.* These vessels may become essential in case of vascular reconstruction or elongation in cases of complex arterial anastomosis, offering the main advantage of better matching of the vascular lumen [160].

e. Excessive perfusion of abdominal organs with preservation solution following aortic cross-clamp through the distal abdominal aorta should be avoided. It is recommended to adhere to the manufacturer's instruction (e.g. maximum volume per kg body weight as well as duration of flush).

f. Particularly in congenital heart defects, longer vascular cuffs may be needed, which could compromise the lung procurement. This situation must be considered at the time of organ recovery co-ordination to avoid misunderstanding between transplant teams.

g. The closure of abdomen and chest should be performed accurately, taking care to recognise cosmetic aspects using intracutaneous skin suture. Ultimate respect of the donor and their family, recognising the immense debt of gratitude owed to them, is essential.

14.9.2. Kidney procurement and transplantation from paediatric deceased donors

Paediatric kidneys can be procured singularly (standard technique) or *en bloc*. Particular care should be taken in children to keep enough aortic and inferior vena cava (suprarenal and infrarenal) length without compromising the coeliac trunk and the infrahepatic inferior vena cava that is usually needed for the liver graft. This represents a major technical problem in the case of a very small donor where the suprarenal stumps of the aorta and inferior vena cava are very short and cannot be simply oversewn on the back table without causing a stenosis of arterial inflow or venous outflow. If the suprarenal inferior vena cava and aortic stumps are too short, it is recommended to procure additional arterial and venous conduits (i.e. thoracic aorta and superior vena cava) to perform an elongation of the above-mentioned stumps or to build a 'cap' on their proximal stump.

Unfortunately, most kidneys from paediatric donors weighing less than 10 kg are usually procured *en bloc* and both offered to one recipient (usually an adult). Considering the rarity of such donors and the problem of size mismatch, when offering a big kidney to a smaller paediatric recipient, one should keep in mind that a kidney from a smaller paediatric donor (i.e. < 10 kg) can be transplanted singularly into a smaller paediatric recipient. This requires significant technical skills when dealing with microvascular surgery [161-162].

Kidney outcomes can have variable results depending on the type of graft (single or *en bloc*), donor

and recipient age (paediatric or adult) [161], kidney donor risk index, HLA mismatches, donor-specific antibodies and underlying kidney disease. Although patient survival following paediatric kidney transplantation is excellent (i.e. 90-95 % at 10 years), the estimated half-life for transplanted kidneys in children is only 9 to 15 years. Therefore, children affected with end-stage renal disease often require more than one kidney transplant in their lifetime [163-164]. In particular, adolescents (11 to 17 years), who account for > 50 % of the paediatric kidney transplant waiting list, have worse 5-year graft survival outcomes than paediatric recipients under the age of 11 [164]. A 10-year graft loss around 52 % after deceased donor kidney transplantation has been reported. Non-adherence to immunosuppression (and other therapies) remains a significant problem among paediatric renal transplant recipients. Estimates of non-adherence range from 30 % to 70 % among paediatric patients. Research demonstrates that a 10 % decrement in adherence is associated with 8 % higher hazard of graft failure and mortality [165].

Naderi *et al.* reported 1-, 5-, 10- and 20-year mean graft survival rates of 90 %, 81 %, 62 % and 62 %, respectively. The corresponding patient survival rates were 100 %, 99.4 %, 97.8 % and 96.5 % [166].

The most relevant surgical complications are represented by reflux nephropathy, which may compromise graft quality if sustained for a long period of time, and vascular complications. These occur mainly in cases of single kidney transplantation from small donors (i.e. < 10 kg) in small recipients (i.e. < 10 kg).

14.9.3. Liver procurement and transplantation from paediatric deceased donors

The same technique of liver procurement used in adults can also be used in children [159].

It should be remembered that paediatric livers can be split (usually from donors > 8 years of age) and this opportunity should be seriously considered for both *in situ* and *ex situ* split-liver procedures according to local split-liver policy, logistics and facilities [159, 167-168].

Children receive whole and split-liver grafts. Transplant outcomes may be different in terms of graft survival that are related to the specific complications inherent to the graft type, donor age and donor risk index. Whole liver transplantation from a paediatric donor into a small paediatric recipient has high rates of vascular complications, which compromise the graft survival [167, 169-170].

In general, 1-, 5- and 10-year patient and graft survival rates after deceased donor liver transplantation in children are 94 %, 90 %, and 87 % (for patients) and 90 %, 85 % and 80 % (for grafts). Major complications include hepatic artery thrombosis (range 5-15 %), portal vein thrombosis (range 1-5 %) and biliary complications (5-15 %) [169-174]. Vascular complications occur more often in the case of small grafts in small recipients. Biliary complications, usually in form of late anastomotic strictures, occur more often in split-liver transplant; they are probably due to long cold ischaemia times and devascularisation of the hilar plate during the split procedure.

14.9.4. Pancreas procurement and transplantation from paediatric deceased donors

Pancreas procurement should rely on standards reported by Nadalin *et al.* [159]. The following aspects of paediatric pancreas transplantation should be considered:

- There is no lower age limit of acceptance of pancreas from paediatric donors, but a lower age limit of 6 years should be considered [175].
- Pancreas procurement should not compromise the ability to transplant the liver (e.g. avoid dividing the gastroduodenal artery direct on the common hepatic artery).

Pancreas transplantation in children is a very rare event. However, pancreases recovered from children are transplanted more and more often in young adult recipients, with excellent graft outcomes and organ growth with time [175-177]. Spaggiari *et al.* have reported 63 pancreas transplantations (28 simultaneous pancreas–kidney transplantation; 17 pancreas-alone and 18 pancreas after kidney transplantation) from paediatric donors. Excellent metabolic control was achieved in 59 (93.6 %) patients at the time of discharge and at 5-year follow-up. Overall patient survival ranged between 87 % and 94 % according to donor age, with a median follow-up of 37.07 months. Overall graft survival was 85.7 % [177].

14.9.5. Intestinal and multivisceral procurement and transplantation from paediatric deceased donors

The standard technique of intestinal and multivisceral procurement in adults can be applied in children [159]. It should be noted that in contemporary abdominal transplantation we are referring to intestinal transplantation and not small bowel transplantation. Whenever possible the intestinal graft should include the ileo-caecal portion and possibly the right

hemi-colon as well. To accomplish this, the middle colic artery should also be recovered. This may compromise the integrity of the inferior pancreatoduodenal artery with consequent potential alteration of arterial perfusion of pancreatic head. In other words, this means that, in the case of extended intestinal procurement, the vascular anatomy of the pancreas (head) can be compromised. The centre accepting the pancreas should be informed of this anatomical challenge before starting organ recovery [159].

The long-term results of paediatric intestinal transplantation including intestine alone, or combined with liver or multivisceral, are actually quite poor. Raghu *et al.* have reported results from the international intestinal transplant registry and showed (overall) 1-year and 5-year graft survival rates of 66.1 % and 47.8 %. Overall, 1-year and 5-year patient survival rates were 72.7 % and 57.2 %. Causes of death were primarily sepsis, graft failure, post-transplant lymphoproliferative disorders/lymphomas and graft-*versus*-host disease [178]. For this reason, the main therapy of intestinal failure in children is represented by intestinal rehabilitation and adaptation associated with long-term parenteral nutrition [179].

14.9.6. Heart procurement and transplantation from paediatric deceased donors

Although the standard rules and procedures for heart procurement in adults may apply [180], there are an important number of recipients (39 %) who suffer from congenital heart disease [181]. This implies the need for complex vascular reconstructions during transplantation [182]. When procuring the heart, we suggest not only cutting the superior vena cava, but dissecting and ligating the azygos vein, and procuring the innominate vein. In the same way, complex arterial reconstruction may need to use part or all of the aortic arch within all its supra-aortic branches. If lung recovery is not planned, pulmonary arteries should be dissected to their first lobar bifurcation, to be used after if the recipient's pulmonary arteries have already been heavily stented. When cutting off the inferior vena cava, a gentle but firm pull should be applied to obtain as much vessel length as possible, within the actual limit of the pericardium and the diaphragm. Finally, a large pericardial patch may be recovered, to be used if further reconstructions should be carried out.

The shortage of younger heart donors has led to the development of ABO-incompatible heart transplant programmes around the world, limiting this resource to children under 14 months, due to ABO antibody presence [183].

The long-term results of paediatric heart transplantation are now well documented [181]. The outcomes show an in-hospital mortality of 12 %, with a survival rate at 1, 5 and 10 years of 90 %, 83 % and 76 % respectively. There is an increasing trend towards the use of mechanical heart assist devices, occurring in up to 38 % of recipients, as well as a growing number of patients (70 %) that have already undergone a previous thoracic surgery [181]. The profile of heart recipients is pointing to a more complex patient, who may need some kind of circulatory assist device prior to transplantation.

Regarding how the donor characteristic may influence the post-transplant primary graft dysfunction incidence, both donor age < 1 year and heart ischaemic time > 4 hours were associated with a higher incidence of dysfunction, whereas donor left ventricular ejection fraction < 45 % and donor support using multiple inotropes did not make dysfunction more likely [184].

14.9.7. Lung procurement and transplantation from paediatric deceased donors

The same donor selection criteria used in adults can also be used in children. The main difference between adult and paediatric donors is sizing. While in adults predicted total lung capacity is the best value for matching donor and receptor, in children height is a more accurate value. Total lung capacity does not change with height in a linear fashion. Children have an increased thoracic compliance and may accommodate more variations in lung size [185-187].

Different strategies have been applied to optimise the lung donor pool in paediatrics. These include the use of cuffed endotracheal tubes to avoid aspiration, HRT, early bronchoscopy when possible, alveolar recruitment manoeuvres, careful fluid therapy management and protective lung ventilation strategies [126]. At the time of the procurement, one of the basic pre-operative steps in adults is a fibre bronchoscope exploration. Often this technique will not be possible, especially in small babies, due to the small size of the endotracheal tube or because of the clinical instability of the patient. It is in this scenario when surgeons will have to pay special attention to the condition of the lungs and airway as a first stage during open surgery.

Intra-operative steps of the lung procurement surgery are almost the same as those described for adult patients. In the case of *en bloc* double lung transplant, bronchial arteries will need to be dissected with a descending aorta patch [188].

The International Thoracic Organ Transplant

Registry of the International Society of Heart and Lung Transplantation shows that the survival rate after lung transplant in adults is around 50 % at 6.2 years; in children it is 50 % at 5.7 years. Paediatric survival rate after heart–lung transplant due to cystic fibrosis is 50 % at 4.0 years, and for idiopathic pulmonary arterial hypertension is 50 % at 6.0 years [189].

14.10. Conclusions

There is a pressing need to increase the probability of access to transplantation for groups of patients with special difficulties due to their characteristics. This is especially true for paediatric patients. The lower probability of receiving a transplant in the child population leads to higher mortality than that observed in the adult population, especially for children < 1 year of age. Paediatric donation is required not only to satisfy the transplantation needs of paediatric – and adult – patients, but also to offer children and their families a unique opportunity at the end of a child's life.

Paediatric donation poses unique challenges, but it remains an under-addressed topic of research and public commentary internationally. This contributes to a lack of awareness among policy makers, health professionals and the public regarding opportunities to establish or improve donation programmes. Paediatric medical specialists and paediatric transplant surgeons should be educated to participate actively in paediatric donation programmes and collaborate with donor co-ordinators and OPOs.

Although most organs recovered for transplantation from adults and children are from BD donors, the increasing rate of DCD indicates an evolving pattern of donor potential, especially in children. Neonatal and paediatric DCD can expand donation and recovery of more organs that can help increase and improve transplant options for many children and adults.

International data suggest missed donation opportunities to identify paediatric donors at EOL, resulting in missed referrals and opportunities for donation. It is a necessity to maximise the recovery of organs from all potential donors to increase the existing donor pool. Preserving the option of donation at EOL is a priority and part of a continuum of care that should be standard and not an exception. The importance of providing expert medical care and emotional support for children and their families throughout the EOL, including donation where relevant, is consistent with ethically informed evidence-based and consensus-based guidelines and policies.

Early identification of potential eligible deceased organ donors must involve rigorous medical management and preservation strategies to maintain the option of donation. Restoration of the normal physiology results in better organ viability, better quality organs being recovered and an improvement in transplantation outcomes.

Transplantation remains an accepted treatment for end-stage organ failure. Transplantation in children and infants requires special considerations because of mismatch in donor and recipient size, and specific indications that are unique to children, including congenital abnormalities of the kidney and urinary tract for renal transplantation, biliary atresia for liver transplantation and congenital heart disease for cardiac transplantation.

Experience with organs recovered from DCD donors and transplanted to children continues to increase. Paediatric DCD renal transplant outcomes continue to show good short- and long-term graft function. Graft survival with transplanted DCD livers has shown good short-term results; however, more information is needed on long-term survival, emphasising the importance of detailed collaborative research. Expanding the use of DCD hearts and lungs along with *in situ* and *ex situ* perfusion may provide additional organs with improved function from this population of patients. Other exciting areas that are evolving in paediatric donation and transplantation include vascularised composite allografts, including limb and abdominal wall transplantation in children [190].

Research agenda

From the literature and discussion of the available evidence, several topics have been identified for which evidence is inconsistent, insufficient or non-existent. The authors of this guide recommend that future research, where possible in well-designed randomised clinical trials, should focus on the following research gaps:

1 Determine barriers to identifying donation opportunities by paediatric critical care professionals and medical teams.
2 Identify and assess the best clinical triggers for paediatric and neonatal donor identification and referral.
3 Identify the best practices to ensure that all patients who are potential BD and DCD donors are referred to the donor co-ordinator/OPO for donation consideration.
4 Determine the best way to train paediatric healthcare professionals to proactively participate in paediatric donation programmes.
5 Develop a quality management system for paediatric donation at local, regional and national

levels that includes quality improvement criteria, quality indicators and systematic internal and external donor auditing to monitor organ donation potential and the donation process.
6 Investigate the physiology of the dying for paediatric patients after WLST.
7 Study the use of steroids, vasopressin and/or thyroid hormones during paediatric donor treatment.
8 Enhance research to increase donation data through a collaborative multicentre outcome-based research project.
9 Study effects of functional and absolute warm ischaemic time for pDCD organs, including outcomes of graft function from pDCD recovered organs.
10 Examine the application of *in situ* and *ex situ* organ support technology in paediatric donation.

14.11. References

1. Davies R. New understandings of parental grief: literature review. *Journal of Advanced Nursing* 2004; 46: 506-13.
2. Arnold J, Buschman PG. The continuing process of parental grief. *Death Studies* 2008;32:658-73.
3. Mahillo B, Carmona M, Álvarez M *et al.* Global database on donation and transplantation: goals, methods and critical issues. *Transplant Rev (Orlando).* 2013; 27(2):57-60.
4. Memoria actividad donación y trasplante. España 2019. Organización Nacional de Trasplantes, available at www.ont.es/infesp/Memorias/ACTIVIDAD%20DE%20DONACI%C3%93N%20Y%20TRASPLANTE%20ESPA%C3%91A%202019.pdf, accessed 7 August 2021.
5. Organ Procurement and Transplantation Network. National Data, available at https://optn.transplant.hrsa.gov/data/view-data-reports/national-data/#, accessed 18 July 2021.
6. Agencie de la Biomedicine. Le rapport médical et scientifique du prélèvement et de la greffe en France 2018. Le prélèvement d'organes en vue de greffe, available at https://rams.agence-biomedecine.fr/sites/default/files/pdf/2019-09/RAMS_2018%20Prelevement.pdf, accessed 18 July 2021.
7. NHS Blood and Transplant. Organ donation and transplantation. Activity report 2018/19 [available at https://nhsbtdbe.blob.core.windows.net/umbraco-assets-corp/16537/organ-donation-and-transplantation-activity-report-2018-2019.pdf, accessed 18 July 2021.
8. ANZOD Registry. 2019 Annual report, Section 4: Deceased organ donor profile. Australia and New Zealand Dialysis and Transplant Registry, Adelaide, Australia. 2019, available at: www.anzdata.org.au/report/anzod-annual-report-2019, accessed 18 July 2021.
9. Annual report 2018. Eurotransplant International Foundation, ed. Peter Branger and Undine Samuel. Leiden. ISBN-EAN: 978-90-71658-38-9, available at www.eurotransplant.org/wp-content/uploads/2019/12/032675-_ET_Jaarverslag_2018_v7-1.pdf, accessed 18 July 2021.
10. Martin DE, Nakagawa TA, Siebelink MJ *et al.* Pediatric deceased donation – a report of the Transplantation Society meeting in Geneva. *Transplantation* 2015; 99: 1403-9.
11. Weiss MJ, Dominguez-Gil B, Lahaie N *et al.* Development of a multinational registry of pediatric deceased organ donation activity. *Pediatr Transplant* 2019; e13345. https://doi.org/10.1111/petr.13345 .
12. UK Donation Ethics Committee. Ethical issues in paediatric organ donation – a position paper by the UK Donation Ethics Committee, (UKDEC) 2015 Jun, pp. 1-23, available at www.aomrc.org.uk/wp-content/uploads/2016/04/Paediatric_organ_donation_position_0615-2.pdf, accessed 18 July 2021.
13. American Academy of Pediatrics. Committee on Hospital Care, Section on Surgery, Section on Critical Care. Pediatric organ donation and transplantation. *Pediatrics* 2010;125:822.
14. Siebelink MJ, Albers MJ, Roodbol PF *et al.* Key factors in paediatric organ and tissue donation: an overview of literature in a chronological working model. *Transpl Int* 2012; 25:265-71.
15. *Newsletter Transplant* 2019. International figures on donation and transplantation 2018, ed. Beatriz Dominguez-Gil. Published jointly with the European Directorate for the Quality of Medicines & HealthCare of the Council of Europe (EDQM). ISSN: 2171-4118, Council of Europe and Organización Nacional de Trasplantes 2019, available at https://register.edqm.eu/freepub (free access), accessed 18 July 2021.
16. Infant mortality in the EU. Mortality and life expectancy statistics. Eurostat, available at https://ec.europa.eu/eurostat/statistics-explained/index.php?title=Mortality_and_life_expectancy_statistics#Infant_mortality, accessed 18 July 2021.
17. Child Trends (2019). Infant, child, and teen mortality. Bethesda MD: Author, available at www.childtrends.org/indicators/infant-child-and-teen-mortality, accessed 18 July 2021.
18. Burns JP, Sellers DE, Meyer EC *et al.* Epidemiology of death in the PICU at five U.S. teaching hospitals. *Crit Care Med* 2014;42:2101-8.
19. Weiss MJ, Perez Blanco A, Gelbart B. Special issues in pediatric deceased organ donation. *Intensive Care Med* 2019; 45:361-3. https://doi.org/10.1007/s00134-019-05523-2.

20. Nakagawa TA, Shemie SD, Dryden-Palmer K *et al.* Organ donation following neurologic and circulatory determination of death. *Pediatr Crit Care Med* 2018; 19:S26-S32.
21. Hawkins KC, Scales A, Murphy P *et al.* Current status of paediatric and neonatal organ donation in the UK. *Arch Dis Child* 2018;103:210-15.
22. Squires JE, Coughlin M, Dorrance K *et al.* Criteria to identify a potential deceased organ donor: a systematic review. *Crit Care Med* 2018;46(8):1318-27.
23. Stiers J, Aguayo C, Siatta A *et al.* Potential and actual neonatal organ and tissue donation after circulatory determination of death. *JAMA Pediatr* 2015;169(7):639-45. https://doi.org/10.1001/jamapediatrics.2015.0317.
24. Weiss MJ, Hornby L, Rochwerg B *et al.* Canadian Guidelines for controlled pediatric donation after circulatory determination of death-summary report. *Pediatr Crit Care Med* 2017;18(11):1035.
25. Gries CJ, White DB, Truog RD *et al.* An Official American Thoracic Society/International Society for Heart and Lung Transplantation/Society of Critical Care Medicine/Association of Organ and Procurement Organizations/United Network of Organ Sharing Statement: Ethical and policy considerations in organ donation after circulatory determination of death. *Am J Respir Crit Care Med* 2013;188:103-9.
26. The American Academy of pediatrics committee on bioethics. Policy statement Ethical controversies in organ donation after circulatory death. *Pediatrics* 2013;131:1021-6.
27. UK Donation Ethics Committee. Organ donation from infants with anencephaly – guidance from the UK Donation Ethics Committee, 2016, available at http://aomrc.org.uk/wp-content/uploads/2016/06/Organ_Donation_-infants_anencephaly_020316-2.pdf, accessed 17 July 2021.
28. Espnic (European Society of Paediatric and Neonatal Intensive Care). Espnic standards for end of life care 2017, available at https://espnic-online.org/Media/Files/Espnic-Standards-for-End-of-Life-Care, accessed 17 July 2021.
29. Siebelink MJ, Geerts EA, Albers MJ *et al.* Children's opinions about organ donation: a first step to assent? *Eur J Public Health* 2012;22:529.
30. Hoover SM, Bratton SL, Roach E *et al.* Parental experiences and recommendations in donation after circulatory determination of death. *Pediatr Crit Care Med* 2014;15:105.
31. O'Malley P, Barata I, Snow S *et al.* Death of a child in the emergency department. *Pediatrics* 2014;134:e313.
32. Bennett EE, Sweney J, Aguayo C *et al.* Pediatric organ donation potential at a children's hospital. *Pediatr Crit Care Med* 2015;16(9):814-20.
33. Siebelink MJ, Albers MJ, Roodbol PF *et al.* Children as donors: a national study to assess procurement of organs and tissues in pediatric intensive care units. *Transpl Int* 2012; 25:1268.
34. Charles E, Scales A, Brierley J. The potential for neonatal organ donation in a children's hospital. *Arch Dis Child Fetal Neonatal* 2014;99:F225.
35. Hanley H, Kim S, Willey E *et al.* Identifying potential kidney donors among newborns undergoing circulatory determination of death. *Pediatrics* 2014;133:e82.
36. Meert KL, Keele L, Morrison W *et al.*; Eunice Kennedy Shriver National Institute of Child Health and Human Development Collaborative Pediatric Critical Care Research Network. End-of-life practices among tertiary care PICUs in the United States: a multicenter study. *Pediatr Crit Care Med* 2015;16:e231-8. https://doi.org/10.1097/PCC.
37. Kirschen, MP, Francoeur C, Murphy M *et al.* Epidemiology of brain death in pediatric intensive care units in the United States. *JAMA Pediatr* 2019;173(5):469-76. https://doi.org/10.1001/jamapediatrics.2019.0249.38.
38. Agra-Tuñas C, Rodriguez-Ruiz E, Rodríguez-Merino E, on behalf of the MOdos de Morir en UCI Pediátrica-2 (MOMUCI-2) study group of the Spanish Society of Paediatric Intensive Care (SECIP). How do children die in PICUs nowadays? A multicenter study from Spain. *Pediatr Crit Care Med* 2020 Sep;21(9):e610-e616. https://doi.org/10.1097/PCC.0000000000002359.
39. ONT (Organización Nacional de Trasplantes). Memoria del Programa de Garantía de Calidad 2018 [in Spanish], available at www.ont.es/infesp/Paginas/ProgramadeGarantiadeCalidad.aspx, accessed 17 July 2021.
40. Corkery-Lavender T, Millar J, Cavazzoni E and Gelbart B. Patterns of organ donation in children in Australia and New Zealand. *Crit Care Resusc* 2017;19: 296-302.
41. Weiss MJ, Hornby L, Witterman W and Shemie SD. Pediatric donation after circulatory determination of death: a scoping review. *Pediatr Crit Care Med* 2016; 17:e87-e108.
42. Rodríguez Núñez A, Pérez Blanco A y Grupo de Trabajo de la AEP-ONT. National recommendations on pediatric donation. *An Pediatr* [English edn] 2020;93(2): 134.e1-9. https://doi.org/10.1016/j.anpedi.2020.04.024.
43. Labrecque M, Parad R, Gupta M, Hansen A. Donation after cardiac death: the potential contribution of an infant organ donor population. *J Pediatr* 2011 Jan; 158(1):31-6.
44. Nakagawa TA, Ashwal S, Mathur M *et al.* Clinical report – Guidelines for the determination of brain death in infants and children: an update of the 1987 task force recommendations. *Pediatrics* 2011;128:e720.
45. RCPCH (Royal College of Paediatrics and Child Health). The diagnosis of death by neurological

criteria (DNC) in infants less than two months old, 2015, available at www.rcpch.ac.uk/system/files/protected/page/DNC%20Guide%20FINAL.pdf, accessed 1 June 2020.

46. Mazille N, Litzler-Renault S, Weider I *et al.* Palliative care for newborns: practices in a level-III unit during a 5-year period [in French]. *Arch Pediatr* 2014;21(2): 177-83.
47. Hanley H, Kim S, Willey E *et al.* Identifying potential kidney donors among newborns undergoing circulatory determination of death. *Pediatrics* 2014;133:e82.
48. Truog RD, Miller FG, Halpern SD. The dead-donor rule and the future of organ donation. *N Engl J Med* 2013;369:1287.
49. Boucek MM, Mashburn C, Dunn SM *et al.* Pediatric heart transplantation after declaration of cardiocirculatory death. *N Engl J Med* 2008;359:709.
50. Kleinmahon JA, Patel SS, Auerbach SR *et al.* Hearts transplanted after circulatory death in children: Analysis of the International Society for Heart and Lung Transplantation registry. *Pediatr Transplant* 2017;21: e13064, https://doi.org/10.1111/petr.13064.
51. Meyburg J, Opladen T, Spiekerkötter U *et al.* Human heterologous liver cells transiently improve hyperammonemia and ureagenesis in individuals with severe urea cycle disorders. *J Inherit Metab Dis* 2018;41(1): 81-9.
52. Smets F, Dobbelaere D, McKiernan P *et al.* Phase I/II Trial of liver derived mesenchymal stem cells in pediatric liver based metabolic disorders: a prospective, open label, multicenter, partially randomized, safety study of one cycle of heterologous human adult liver-derived progenitor cells (HepaStem®) in urea cycle disorders and Crigler-Najjar Syndrome patients. *Transplantation* 2019 Sep;103(9):1903-15. https://doi.org/10.1097/TP.0000000000002605.
53. Curley MA, Harrison CH, Craig N *et al.* Pediatric staff perspectives on organ donation after cardiac death in children. *Pediatr Crit Care Med* 2007;8:212.
54. Bellali T, Papadatou D. The decision-making process of parents regarding organ donation of their brain dead child: a Greek study. *Soc Sci Med* 2007;64:439.
55. Brierley J. Pediatric organ donation in the UK. *Arch Dis Child* 2010;95:83-8. https://doi.org/10.1136/adc.2009.168716.
56. De la Rosa G, Domínguez-Gil B, Matesanz R *et al.* Continuously evaluating performance in deceased donation: the Spanish quality assurance program. *Am J Transplant* 2012;12:2507-13. https://doi.org/10.1111/j.1600-6143.2012.04138.x.
57. Truog RD. Pediatric donation after circulatory determination of death: Canadian Guidelines define parameters of consensus and uncertainty. *Pediatr Crit Care Med* 2017;18:1068-70. https://doi.org/10.1097/PCC.0000000000001322.
58. ACRE Trial Collaborators. Effect of 'collaborative requesting' on consent rate for organ donation: Randomised controlled trial (ACRE trial). *BMJ* 2009;339: b3911.
59. Rodrigue JR, Cornell DL, Howard RJ. Pediatric organ donation: what factors most influence parents' donation decisions? *Pediatr Crit Care Med* 2008;9(2):180-5.
60. Domínguez-Gil B, Coll E, Elizalde J *et al.* Expanding the donor pool through intensive care to facilitate organ donation: results of a Spanish multicenter study. *Transplantation* 2017;101(8):e265-72.
61. Hulme W, Allen J, Manara AR *et al.* Factors influencing the family consent rate for organ donation in the UK. *Anaesthesia* 2016;71(9):1053-63.
62. Jansen NE, van Leiden HA, Haase-Kromwijk BJ *et al.* Appointing 'trained donation practitioners' results in a higher family consent rate in the Netherlands: a multicenter study. *Transpl Int* 2011;24:1189-97.
63. Siminoff LA, Gordon N, Hewlett J *et al*: Factors influencing families' consent for donation of solid organs for transplantation. *JAMA* 2001;286:71-7.
64. Harrison CH, Laussen PC. Controversy and consensus on pediatric donation after cardiac death: ethical issues and institutional process. *Transplant Proc* 2008;40:1044-7.
65. Brierley J, Hasan A. Aspects of deceased organ donation in paediatrics. *Br J Anaesth* 2012;108(Suppl 1): i92-5.
66. Citerio G, Crippa IA, Bronco A *et al.* Variability in brain death determination in Europe: looking for a solution. *Neurocritical Care* 2014;21:376-82.
67. Wahlster S, Wijdicks EFM, Patel PV *et al.* (2015): Brain death declaration: Practices and perceptions worldwide. *Neurology* 2015;84:1870-9.
68. Shemie SD, Hornby L, Baker A *et al.* The International Guidelines for Determination of Death phase 1 participants, in collaboration with the World Health Organization: International guideline development for the determination of death. *Intensive Care Med* 2014;40:788-97.
69. Gardiner D, Shemie S, Manara A, Opdam H. International perspective on the diagnosis of death. *Br J Anaesth* 2012;108(Suppl 1):i14-28.
70. Lewis A, Bakkar A, Kreiger-Benson E *et al.* Determination of death by neurologic criteria around the world. *Neurology* 2020;95:e299-e309. https://doi.org/10.1212/WNL.0000000000009888.
71. Greer DM, Shemie SD, Lewis A *et al.* Determination of brain death/death by neurologic criteria. The World Brain Death Project. *JAMA* 2020 3 Aug:1-20. https://doi.org/10.1001/jama.2020.11586, including Nakagawa TA, Jacobe S, Greer D *et al.* Pediatric and neonatal

brain death/death by neurologic criteria. Supplement 6 (Supplementary Online Content).

72. Smith M. Brain death: time for an international consensus. *Br J Anaesth* 2012;108(Suppl 1):i6-9.
73. Wijdicks EFM. The transatlantic divide over brain death determination and the debate. *Brain* 2012;135: 1321-31.
74. Österreichisches Bundesinstitut für Gesundheitswesen (ÖBIG), Oberster Sanitätsrat (16.11.2013): Empfehlungen zur Durchführung der Hirntoddiagnostik bei einer geplanten Organentnahme, available at www.goeg.at/de/Bereich/Todesfeststellung.html, accessed 7 August 2021.
75. Unités multidisciplinaires (2007): Transplantation (Centre) Diagnostic de mort encéphalique, available at www.erasme.ulb.ac.be, accessed 7 August 2021.
76. Sundhedsstyrelsen, Dansk Neurokirurgisk Selskabs 'Hjernedødsudvalg' (2013): Konstatering af Hjernedød, available at www.tilogaard.dk/Hjernedoedsundersoegelse_december_2013.pdf, accessed 17 July 2021.
77. Agence de la biomédecine. Recommandations formalisées d'experts sur la prise en charge des patients en vue d'un prélèvement d'organes (donneurs en état de mort encéphalique et à cœur arrêté) 2019, available at www.agence-biomedecine.fr/Recommandations-formalisees-d-experts-sur-le-prelevement-et-la-greffe, accessed 17 July 2021.
78. Bundesärztekammer (30.03.2015). 'Richtlinie gemäß §16 Abs. 1 S. 1 Nr. 1 TPG für die Regeln zur Feststellung des Todes nach §3 Abs. 1 S. 1 Nr. 2 TPG und die Verfahrensregeln zur Feststellung des endgültigen, nicht behebbaren Ausfalls der Gesamtfunktion des Großhirns, des Kleinhirns und des Hirnstamms nach §3 Abs. 2 Nr. 2 TPG' Vierte Fortschreibung. Richtlinie Bundesärztekammer Vierte Fortschreibung, available at www.bundesaerztekammer.de/fileadmin/user_upload/downloads/irrev.Hirnfunktionsausfall.pdf, accessed 17 July 2021.
79. Magyar Közlöny (2012. évi 105. szám). A Kormány tagjainak rendeletei: Az emberi erőforrások minisztere 12/2012. (VIII. EMMI rendelete az egészségügyről szóló 1997. évi CLIV. törvénynek a szerv- és szövetátültetésre, valamint -tárolásra és egyes kórszövettani vizsgálatokra vonatkozó rendelkezései végrehajtásáról szóló 18/1998. (XII. 27.) EüM rendelet módosításáról, available at www.ovsz.hu/sites/ovsz.hu/files/szervadomanyozas_dokumentum/csatolmanyok/tajekoztato_rendelet_modositasrol/18-1998-rendelet-modosito.pdf, accessed 17 July 2021.
80. Monitor Polski, dziennik urzędowy rzeczypospolitej polskiej, Warszawa, dnia 17 stycznia 2020 r., Poz. 73, Obwieszczenie Ministra Zdrowia z dnia 4 grudnia 2019 r., available at https://monitorpolski.gov.pl/M2020000007301.pdf, accessed 17 July 2021.
81. Ministerio de Sanidad, Servicios Sociales e Igualdad (2012). Boletín oficial del Estado Real Decreto 1723/2012, de 28 de diciembre, por el que se regulan las actividades de obtención, utilización clínica y coordinación territorial de los órganos humanos destinados al trasplante y se establecen requisitos de calidad y seguridad. BOE Núm. 313, S., available at www.boe.es/diario_boe/txt.php?id=BOE-A-2012-15715, accessed 17 July 2021.
82. Schweizerische Akademie der Medizinischen Wissenschaften (SAMW) (01.09.2011). Feststellung des Todes mit Bezug auf Organtransplantationen Medizin-ethische Richtlinien, available at www.samw.ch/de/Ethik/Richtlinien/Aktuell-gueltige-Richtlinien.html, accessed 17 July 2021.
83. Academy of Medical Royal Colleges (2008). A code of practice for the diagnosis and confirmation of death, available at www.aomrc.org.uk/reports-guidance/ukdec-reports-and-guidance/code-practice-diagnosis-confirmation-death/, accessed 17 July 2021.
84. RCPCH (Royal College of Paediatrics and Child Health). The diagnosis of death by neurological criteria in infants less than two months old, 2015, available at www.rcpch.ac.uk/improving-child-health/clinical-guidelines-and-standards/published-rcpch/death-neurological-criteria, accessed 17 July 2021.
85. Nakagawa TA, Ashwal S, Mathur M, Mysore M. Committee for Determination of Brain Death in Infants and Children. Guidelines for the determination of brain death in infants and children: an update of the 1987 task force recommendations – executive summary. *Ann Neurol* 2012 Apr;71(4):573-85.
86. Shemie SD, Ross H, Pagliarello J *et al.* Organ donor management in Canada: recommendations of the forum on Medical Management to Optimize Donor Organ Potential. *CMAJ* 2006; 174:S13-32.
87. Kotloff RM, Blosser S, Fulda GJ *et al.* Management of the potential organ donor in the ICU: Society of Critical Care Medicine/American College of Chest Physicians/Association of Organ Procurement Organizations Consensus Statement. *Crit Care Med* 2015; 43(6):1291-1325.
88. Nelson K, Nakagawa TA, Berkowicz I. Organ donation in children. *Rogers' Textbook of Pediatric Intensive Care*. 5th edn, ed. David Nichols and Hal Shaffner, 2015, Wolters Kluwer, Philadelphia PA.
89. Nakagawa TA. The process of organ donation and pediatric donor management. *Furhman Textbook of Critical Care Medicine*. 5th edn, ed. Bradley Fuhrman and Jerry Zimmerman, 2016. Elsevier, Philadelphia PA.

90. DuBose J, Salim A. Aggressive donor management protocol. *J Int. Care Med* 2008;23;6:367-75.
91. Rosendale JD, Kauffman HM, McBride MA *et al.* Agressive pharmacologic donor management results in more transplanted organs. *Transplantation* 2003; 75(4):482-7.
92. Finfer S, Bohn D, Colpitts D *et al.* Intensive care management of paediatric organ donors and its effect on post-transplant organ function. *Intensive Care Med* 1996;22(12):1424-32.
93. Carone L, Alurkar S, Kigozi P *et al.* Organ and tissue donation in a regional pediatric intensive care unit: evaluation of practice. *Eur J Pediatr* 2018;177:709-14.
94. Lutz-Dettinger N, De Jaeger A, Kerremans I. Care of the potential pediatric organ donor. *Pediatric Clinics North America* 2001;48(3):715-49.
95. Bonetto G, Taffarel M, Gamermam M *et al.* Brain death and organ donation in Argentine pediatric intensive care units: a multicenter study. *Arch Argent Pediatr* 2018;116(1):e54-e60 [in Spanish].
96. Pullerits R, Oltean S, Flodén A *et al.* Circulating resisting levels are early and significantly increased in deceased brain dead organ donors, correlate with inflammatory cytokine response and remain unaffected by steroid treatment *J Transl Med* 2015;13:201-8.
97. Tsai E, Shemie SD, Cox PN *et al.* Organ donation in children: role of the pediatric intensive care unit. *Pediatr Crit Care Med* 2000;1:156-60.
98. Gupta R, Dhanani S. Endocrine considerations of the pediatric organ donor. *J Pediatr Intensive Care* 2016; 5:205-12.
99. Davis AL, Carcillo JA, Aneja RK, *et al.* American College of Critical Care Medicine clinical practice parameters for hemodynamic support of pediatric and neonatal septic shock. *Crit Care Med* 2017;45(6): 1061-93.
100. Plurad DS, Bricker S, Neville A *et al.* Arginine vasopressin significantly increases the rate of successful organ procurement in potential donors. *Am J Surg* 2012;204(6):856-861.
101. Beckman EJ. Management of the pediatric organ donor. *J Pediatr Pharmacol Ther* 2019;14(4):276-89.
102. Weiss SL, Peters MJ, Alhazzani W *et al.* Executive summary: Surviving Sepsis Campaign international guidelines for the management of septic shock and sepsis-associated organ dysfunction in children. *Pediatr Critical Care Med* 2020;21(2):186-95.
103. Charpentier J, Cariou A. Objectifs et moyens de la prise en charge hémo-dynamique. In: G Boulard, P Guiot, T Pottecher, A Tenaillon, eds. *Prise en charge des sujets en état de mort encéphalique dans l'optique du prélèvement d'organes et de tissus*. Paris: Elsevier, 2005:125-35.
104. Ream RS, Clark MG, Ambrecht ES. Pediatric donor management goals in use by US Organ Procurement Organizations. *Prog Transplant* 2019;29(2):150-156. https://doi.org/10.1177/1526924819835835.
105. Richmond ME, Easterwood R, Singh RK *et al.* Low-dose donor dopamine is associated with a decreased risk of right heart failure in pediatric heart transplant recipients. *Transplantation* 2016;100(12):2729-34.
106. Schnülle P, Gottmann U, Hoeger S *et al.* Effects of donor pretreatment with dopamine on graft function after kidney transplantation: a randomized control trial. *JAMA* 2009;302:1067-75.
107. Benck U. Donor dopamine does not affect liver graft survival: evidence of safety from a randomized controlled trial. *Liver Transplant* 2018;24:1336–1345.
108. Ball IM, Hornby L, Rochwerg B *et al.* Management of the neurologically deceased organ donor: a Canadian clinical practice guideline. *CMAJ* 2020;192:E361-9.
109. Katz K, Lawler J, Wax J *et al.* Vasopressin pressor effects in critically ill children during evaluation for brain death and organ recovery. *Resuscitation* 2000; 47(1):33-40.
110. Dujardin KS, Mc Cully RB,Wijdicks EFM *et al.* Myocardial dysfunction associated with brain death: clinical, echocardiographic, and pathologic features. *J Heart Lung Transplant* 2001;20:350-7.
111. Paul JJ, Llyod YT, Shaddy RE, Minich LLA. Spectrum of left ventricular dysfunction in potential pediatric heart transplant donors. *J Heart Lung Transplant* 2003;22(5):548-52.
112. Ktishnamoothy V, Prathep S, Sharma D *et al.* Cardiac dysfunction following brain death after severe pediatric traumatic brain injury: a preliminary study of 32 children. *Int J Crit Illn Inj Sci* 2015;5(2):103-107.
113. Krishnamoorthy V, Borbely X, Rowhani-Rahbar A *et al.* Cardiac dysfunction following brain death in children: prevalence, normalization, and transplantation. *Pediatric Crit Care Medicine* 2015;16(4):e107-12.
114. Casartelli M, Bombardini T, Simion D *et al.* Wait, treat and see: echocardiographic monitoring of brain-dead potential donors with stunned heart. *Cardiovascular Ultrasound* 2012;10:25.
115. Ferrera R, Hadour G, Tamion F *et al.* Brain death provokes very acute alteration in myocardial morphology detected by echocardiography: preventive effect of beta-blockers. *Transplant Int* 2011;24:300-6.
116. Audibert G, Charpentier C, Seguin-Devaux C *et al.* Improvement of donor myocardial function after treatment of autonomic storm during brain death. *Transplantation* 2006;82(8):1031-6.
117. Cherick WS, Edwards LB, Sweet SC *et al.* The effect of hormonal resuscitation on organ utilization in pediatric donors. Presented at the Pediatric Summit for Organ Donation and Transplantation, OPTN. San Antonio TX, 2007.

118. Zambergs K, Vyas H. Management of potential organ donor. *Pediatric and Child Health* 2015;25(5):234-8. https://doi.org/10.1016/j.paed.2015.01.004.
119. Uribe M, Alba A, González G *et al.* Pediatric liver transplant outcome using severe hypernatremic donors. *Transplant Proc* 2013;45(10):3726-7. https://doi.org/10.1016/j.transproceed.2013.08.078.
120. Kaseje N, McLin V, Toso C *et al.* Donor hypernatremia before procurement and early outcomes following pediatric liver transplantation. *Liver Transpl* 2015; 21(8):1076-81. https://doi.org/10.1002/lt.24145.
121. Choong K, Bohn D, Fraser DD *et al.* Canadian Critical Care Trials Group: Vasopressin in pediatric vasodilatory shock: a multicenter randomized controlled trial. *Am J Respir Crit Care Med* 2009;180:632-9.
122. Zuppa AF, Nadkarni V, Davis L *et al.* The effect of a thyroid hormone infusion on vasopressor support in critically ill children with cessation of neurologic function. *Crit Care Med* 2004;32(11):2318-22.
123. Dupuis S, Amiel J-A, Desgroseilliers M *et al.* Corticosteroids in the management of brain death potential organ donors: a systematic review. *Br J Anaesth* 2014; 113(3):346-59. https://doi.org/10.1093/bja/aeu154.
124. Mojtabaee M, Sadegh Beigee F, Ghorbani F. Deceased organ donation from pediatric donors; does the literature really help us? Implication for more powerful guidelines. *Transplant Proc* 2017;49(8):1708-11. https://doi.org/10.1016/j.transproceed.2017.06.039.
125. Mehrotra S, Misir A. Special traumatized populations: accidental hypothermia in children. *Current Ped Reviews* 2018;14:28-33.
126. Mallory GB, Schecter MG, Elidemir Okan. Management of the pediatric organ donor to optimize lung donation. *Pediatric Pulmonology* 2009;44:536-46.
127. Mascia L, Pasero D, Slutsky AS *et al.* Effect of a lung protective strategy for organ donors on eligibility and availability of lungs for transplantation: a randomized controlled trial. *JAMA* 2010;304(23):2620-7.
128. Lele AV, Nair BG, Fong C *et al.* Anesthetic management of brain death adult and pediatric organ donors: the Harborview medical center experience. *J Neurosurg Anesthesiol* 2020. https://doi.org/10.1097/ANA.0000000000000683.
129. Doctor A, Cholette JM, Remy K *et al.* Recommendations on red blood cell transfusion in general critically ill children based on hemoglobin and/or physiologic thresholds from the pediatric critical care transfusion and anemia expertise initiative. *Pediatr Crit Care Med* 2018;19(9):S98-S113.
130. Sharma TS, Michaels MG, Danziger-Izakov L *et al.* Clinical vignettes: donor-derived infections. *J Ped Infect Dis Soc* 2018;7(S2):S67-71.
131. Kaul D, Tlusty S, Wilk A *et al.* A report of the OPTN Ad Hoc Disease Transmission Advisory Committee. Boston: American Transplant Congress 2016.
132. Smith CJ, McCulloch MA, Shirley D-A *et al.* Pediatric heart transplant from an incompletely treated influenza A-positive donor. *Pediatric Transplantation* 2019; 23:e13585.
133. Isnardi DI, Olivero F, Lerda R *et al.* Extracorporeal membrane oxygenation as a bridge to organ donation: a case report. *Transplant Proc* 2013;45(7):2619-20.
134. Bode H, Sauer M, Pingsheim W. Diagnoses of brain death by transcranial Doppler sonography. *Arch Dis Child* 1988;63:1474-8.
135. Olgun G, Newey CR, Ardelt A. Pupillometry in brain death: differences in pupillary diameter between paediatric and adult subjects. *Neurological Research* 2015; 37(11):945-50.
136. Kuyaz C, Birbicer H, Doruk N, Atici A. Bispectral index in confirmation of brain death in children. *J Child Neurology* 2006;21(9):799-801.
137. Darlington AS, Long-Sutehall T, Duncan R *et al.* Parents' experiences of requests for organ and tissue donation: the value of asking. *Arch Dis Child* 2019;104: 837-43.
138. Odim J, Laks H, Banerji A *et al.* Does duration of donor brain injury affect outcome after orthotopic pediatric heart transplantation? *J Thorac Cardiovasc Surg* 2005;130:187-93.
139. Devictor DJ, Latour JM, Eurydice II study group. Forgoing life support: how the decision is made in European pediatric intensive care units. *Intensive Care Med* 2011;37(11):1881-7.
140. Hessheimer AJ, Dominguez-Gil B, Fondevila C, Matesanz R. Controlled donation after circulatory determination of death in Spain. *Am J Transplant* 2016; 16(7):2239-40.
141. Troppmann C, Santhanakrishnan C, Fananapazir G *et al.* Pediatric en bloc kidney transplantation from very small (≤10 kg) donation after circulatory death (versus brain death) donors: Single-center matched-pair analysis of 130 transplants. *Am J Transplant* 2018; 18(11):2811-17.
142. Greer R, Soar J. Lazarus phenomenon: confirmation of death after unsuccessful cardiopulmonary resuscitation. *Resuscitation* 2013;84(12):e151.
143. Hornby L, Dhanani S, Shemie SD. Update of a systematic review of autoresuscitation after cardiac arrest. *Crit Care Med* 2018;46(3):e268-72.
144. Tibballs J, Russell P. Reliability of pulse palpation by healthcare personnel to diagnose paediatric cardiac arrest. *Resuscitation* 2009;80(1):61-4.
145. Youngner SJ, Arnold RM, Schapiro R. *The definition of death: contemporary controversies*, Baltimore MD: Johns Hopkins University Press, 2002.
146. Carcillo JAJ, Orr RR, Bell MM *et al.* A call for full

public disclosure and moratorium on donation after cardiac death in children. *Pediatr Crit Care Med* 2010 Sep;11(5):641-5.

147. Truog RD, Miller FG. The dead donor rule and organ transplantation. *N Engl J Med* 2008;359(7):674-5.
148. Bernat JL. The boundaries of organ donation after circulatory death. *N Engl J Med* 2008;14;359(7):669-71.
149. Dhanani S, Hornby L, Ward R *et al.* Vital signs after cardiac arrest following withdrawal of life-sustaining therapy: A multicenter prospective observational study. *Crit Care Med* 2014;42(11):2358-69.
150. Ethics Committee, American College of Critical Care Medicine; Society of Critical Care Medicine. Recommendations for nonheartbeating organ donation. A position paper by the Ethics Committee, American College of Critical Care Medicine, Society of Critical Care Medicine. *Crit Care Med* 2001;29(9):1826-31.
151. Brierley J, Shaw D. Premortem interventions in dying children to optimise organ donation: an ethical analysis. *J Med Ethics* 2016;42(7):424-8.
152. Brierley J. Current status of potential organ donation in cases of lethal fetal anomaly. *Obstet Gynecol* 2013; 15(3):184-8.
153. Jivraj A, Scales A, Brierley J. Elective ventilation to facilitate organ donation in infants with anencephaly: perinatal professionals' views and an ethical analysis. *Am J Crit Care* 2016;105(5):494-8.
154. Nakagawa TA, Zollinger C, Chao J *et al.* Anencephalic infants as organ donors. *Transplantation* 2017;101:S2 Suppl 8 S60. https://doi.org/10.1097/o.tp.0000525071.97665.cb.
155. Messer S, Page A, Axell R *et al.* Outcome after heart transplantation from donation after circulatory-determined death donors. *J Heart Lung Transplant* 2017;36(12):1311-18. https://doi.org/10.1016/j.healun.2017.10.021.
156. Manara A, Shemie SD, Large S *et al.* Maintaining the permanence principle for death during *in situ* normothermic regional perfusion for donation after circulatory death organ recovery: a United Kingdom and Canadian proposal. *Am J Transplant* 2020;20: 2017-25. https://doi.org/10.1111/ajt.15775.
157. Nakagawa TA, Bratton SL. Pediatric DCDD, past, present, and hopeful future changes. *Ped Crit Care Med* 2016;17(3):270-1.
158. Otte JB, Squifflet JP, Carlier MC *et al.* Organ procurement in children – surgical, anaesthetic and logistic aspects. *Intensive Care Med* 1989;15(Suppl 1):S67-70.
159. Aseni P, Grande AM, De Carlis L. *Multiorgan procurement for transplantation*, 1st edn. Cham, Switzerland: Springer International Publishing 2016, incl. S. Nadalin *et al.*, 'Pancreas procurement', pp. 165-82.
160. Muiesan P, Rela M, Heaton ND. Use of cadaveric superior mesenteric artery as interpositional vascular graft in orthotopic liver transplantation. *Br J Surg* 2001;88(1):70-2.
161. Weitz M, Laube GF, Schmidt M *et al.* Outcome of renal transplantation in small infants: a match-controlled analysis. *Pediatr Nephrol* 2018;33(6):1057-68.
162. Gallinat A, Sotiropoulos GC, Witzke O *et al.* Kidney grafts from donors </= 5 yr of age: single kidney transplantation for pediatric recipients or en bloc transplantation for adults? *Pediatr Transplant* 2013; 17(2):179-84.
163. Aoki Y, Hamasaki Y, Satoh H *et al.* Long-term outcomes of pediatric kidney transplantation: a single-center experience over the past 34 years in Japan. *Int J Urol* 2020;27(2):172-8.
164. Winterberg PD, Garro R. Long-term outcomes of kidney transplantation in children. *Pediatr Clin North Am* 2019;66(1):269-80.
165. Steinberg EA, Moss M, Buchanan CL, Goebel J. Adherence in pediatric kidney transplant recipients: solutions for the system. *Pediatr Nephrol* 2018;33(3): 361-72. https://doi.org/10.1007/s00467-017-3637-0.
166. Naderi G, Latif A, Karimi S *et al.* The long-term outcome of pediatric kidney transplantation in Iran: results of a 25-year single-center cohort study. *Int J Organ Transplant Med* 2017;8(2):85-96.
167. Gao W, Song Z, Ma N *et al.* Utility of neonatal donors in pediatric liver transplantation: a single-center experience. *Pediatr Transplant* 2019;23(5):e13396.
168. Cescon M, Spada M, Colledan M *et al.* Split-liver transplantation with pediatric donors: a multicenter experience. *Transplantation* 2005;79(9):1148-53.
169. Alexopoulos SP, Nekrasov V, Cao S *et al.* Effects of recipient size and allograft type on pediatric liver transplantation for biliary atresia. *Liver Transpl* 2017; 23(2):221-33.
170. Mogul DB, Luo X, Bowring MG *et al.* Fifteen-year trends in pediatric liver transplants: split, whole deceased, and living donor grafts. *J Pediatr* 2018;196: 148-53 e2.
171. Qian J, Zhou T, Qiu BJ *et al.* Postoperative risk factors and outcome of patients with liver transplantation who were admitted to pediatric intensive care unit: a 10-year single-center review in China. *J Intensive Care Med* 2020 Nov;35(11):1241-9. https://doi.org/10.1177/0885066619849558.
172. Kim SS, Ramos-Gonzalez G, Staffa SJ *et al.* Donor-to-recipient weight ratio is a risk factor for hepatic artery thrombosis after whole-liver transplantation in children under 25 kg. *Pediatr Transplant* 2019: e13623.
173. Zhang R, Zhu ZJ, Sun LY *et al.* Outcomes of pediatric liver transplantation: deceased donor liver transplantation vs living donor liver transplantation. *Transplant Proc* 2018;50(10):3601-5.

174. Cuenca AG, Kim HB, Vakili K. Pediatric liver transplantation. *Semin Pediatr Surg* 2017;26(4):217-23.
175. Biglarnia AR, Bennet W, Nilsson T *et al.* Utilization of small pediatric donors including infants for pancreas and kidney transplantation: exemplification of the surgical technique and the surveillance. *Ann Surg* 2014;260(2):e5-7.
176. Ito T, Kenmochi T, Aida N *et al.* The outcomes of pancreatic transplantation from pediatric donors – a single institution experience. *J Clin Med* 2019;8(9): 1386. https://doi.org/10.3390/jcm8091386.
177. Spaggiari M, Di Bella C, Di Cocco P *et al.* Pancreas transplantation from pediatric donors: a single-center experience. *Transplantation* 2018;102(10):1732-9.
178. Raghu VK, Beaumont JL, Everly MJ *et al.* Pediatric intestinal transplantation: analysis of the intestinal transplant registry. *Pediatr Transplant* 2019;23(8): e13580.
179. Norsa L, Lambe C, Abi Abboud S *et al.* The colon as an energy salvage organ for children with short bowel syndrome. *Am J Clin Nutr* 2019;109(4):1112-18.
180. Krantowitz A, Haller JD, Joos H *et al.* Transplantation of the heart in an infant and an adult. *Am J Cardiol* 1968;22:782-90.
181. Rey J, Polo ML, Sanchez R *et al.* Experience with paediatric heart transplant and in congenital heart disease transplant, our history: 24-years experience. *Cir Cardiov* 2019;26(S1):17-23 [in Spanish].
182. Vouhé PR, Tamisier D, le Bidois J *et al.* Pediatric cardiac transplantation for congenital heart defects: surgical considerations and results. *Ann Thorac Surg* 1993;56(6):1239-47.
183. Urschel S, Larsen IM, Kirk R *et al.* ABO-incompatible heart transplantation in early childhood: an international multicenter study of clinical experiences and limits. *J Heart Lung Transplant* 2013;32:285-92. https://doi.org/10.1016/j.healun.2012.11.022.
184. Profita EL, Gauvreau K, Rycus P *et al.* Incidence, predictors, and outcomes after severe primary graft dysfunction in pediatric heart transplant recipients. *J Heart Lung Transplant* 2019;38(6):601-8.
185. Hwang SH, Lee BG, Kim TH *et al.* Comparision of predicted total lung capacity and total lung capacity by computed tomography in lung transplantation candidates. *Yonsei Med J* 2016;57:963-7.
186. Konheim JA, Kon ZN, Parija C *et al.* Predictive equations for lung volumes from computed tomography for size matching in pulmonary transplantation. *J Thorac Cardiovasc Surg* 2016 Apr;151(4): 1163-9.e1. https://doi.org/10.1016/j.jtcvs.2015.10.051.
187. Mallory GB, Das S, Gazzaneo MC, Melicoff E. *Solid organ transplantation in infants and children*. Chapter on Pediatric lung transplantation: peri-operative management. Addison TX: ISHLT Monograph Series, vol. 13, April 2013.
188. Guzman-Pruneda FA, Orr Y, Trost JG *et al.* Bronchial artery revascularization and en bloc lung transplant in children. *J Heart Lung Transplant* 2016;35:122-9. https://doi.org/10.1016/j.healun.2015.08.010.
189. Hayes D, Cherikh WS, Chambers DC *et al.* The International Thoracic Organ Transplant Registry of the International Society for Heart and Lung Transplantation: Twenty-second pediatric lung and heart-lung transplantation report – 2019; Focus theme: Donor and recipient size match. *J Heart Lung Transplant* 2019;38(10):1015-27. https://doi.org/10.1016/j.healun.2019.08.003.
190. Nakagawa TA, Johnson DE. The growth and impact of pediatric donation in the United States. *Transplantation*. 2020;104(S3):S558.

Related material

Appendix 4. Synopsis of national codes for neurological determination of death in infants and children in 10 European countries
Appendix 7. The use of steroids in the management of deceased donors
Appendix 8. The use of thyroid hormones in the management of deceased donors

Chapter 15. Donation of vascularised composite allografts

15.1. The concept of transplantation of vascularised composite allografts

The use of vascularised composite allografts (VCAs), formally called 'composite tissue allografts (CTAs)', is a growing field of transplantation that has been developing for more than 20 years. The aim of VCA transplantation is to restore and repair, 'like for like', large or severe anatomical defects for patients suffering from severe disabilities that cannot be repaired by conventional plastic reconstructive surgery. VCA transplantation has a primary goal of being life-enhancing, improving the patients' quality of life (QoL), whereas solid organ transplantation is recognised as a life-saving procedure in patients with end-stage organ failure.

Following some previous attempts in the 1960s, successful VCA transplants started in 1998 in France with the first transplantation of unilateral hand [1], followed by the first face transplantation in 2005 [2]. Nowadays, VCA activity is mainly represented by upper extremities and face transplantation, and more recently by uterus transplantation. Beyond those areas, VCAs are transplanted in other parts of the body at a lower frequency: abdominal wall, lower limb, larynx and trachea, and penis (see Table 15.1).

Directive 2010/53/EU [13] defines organs as "a differentiated part of the human body, formed by different tissues, that maintains its structure, vascularisation, and capacity to develop physiological functions with a significant level of autonomy. A part of an organ is also considered to be an organ if its function is to be used for the same purpose as the entire organ in the human body, maintaining the requirements of structure and vascularisation".

VCAs are considered as organs because they involve differentiated parts of the human body, containing different type of tissues such as skin, muscles, bones, tendons and vessels that require surgical connection of blood vessels for allograft function. Once transplanted, they maintain their structure, vascularisation and capacity to develop physiological functions at an autonomous level. They are subject to the same time constraints as organs due to their vulnerability to ischaemia, the absence of storage options and the absolute need for immunosuppressive therapy in the recipient. In many European countries, VCA transplantation is still operating under research protocols, whereas in 2011 the US Department of Health and Human Services announced that VCAs fall under the scope of organ legislation. A regulatory definition was adopted and VCA transplant was considered to be a 'standard procedure of care' covered by the federal regulations (the Organ Procurement and Transplantation Network [OPTN] Final Rule) and legislation (the National Organ Transplant Act), in effect since 3 July 2014 [14].

15.2. Special issues in donation of grafts for upper extremity and face transplantation

15.2.1. Activity of upper extremity and face transplantation

To our knowledge, 113 upper extremity transplantations (UETs) have been performed in 28 centres (43.1 % unilateral and 56.9 % bilateral), and there have been 44 cases of total or partial face transplantation (FT) performed in 22 centres worldwide [15]. Without a mandatory requirement to report all procedures at a supranational level, it is still difficult to provide accurate data. Since 2002, the International Registry on Hand and Composite Tissue Transplantation (IRHCTT) has collected information on a voluntary basis. The IRHCTT includes 91 % of UETs and 81 % of FTs performed worldwide except for Chinese recipients [15].

15.2.1.1. *Upper extremity transplantation*

UET is usually carried out by plastic hand surgeons in a comparable fashion to replantation surgery. The principal causes of amputation are explosion, crush injury, electrocution, clean-cut lesions and sepsis [15, 16]. The level of amputation is usually distal (palmar, wrist and distal forearm) but several arm transplants have also been performed [15-19]. Some countries have adopted a national agreement authorising exclusively bilateral UET, taking into consideration the possibility of overcoming the handicap in cases of unilateral amputation and also the potential negative psychological impact when the patient observes differences between the native and transplanted limbs [20-21].

Despite sustained immunosuppressive therapy, the majority of recipients (87.8 %) experienced skin acute rejection (AR) episodes (0 to 12; median 3) during the follow-up period, which ranged from 6 months to 18 years. To date, 13.4 % upper extremity transplanted patients have developed signs of chronic rejection or graft vasculopathy, macroscopically detected on the skin [15, 22]. Under-immunosuppression seemed to be the principal cause, mainly due to poor compliance with immunosuppressive treatment [23]. However, the risk of late deterioration or graft loss may persist despite optimal immunosuppression, as in solid organ transplantation [24]. The collected data show that hand allograft recipients developed metabolic disorders, opportunistic infections and malignancies [18, 25]. More data are needed for comparison with solid organ transplant complications. The IRHCTT reports a patient survival rate of 96.7 % at 10 years. Graft survival in UET is currently 86.6 % at 10 years [15]. A few attempts to reconstruct large body defects, like combined face and hand transplants or quadri-membral transplantation have not succeeded so far, due to severe infection and surgical failure [26-27].

Table 15.1. **VCA graft transplantations that are less often performed**

Kind of VCA	Remarks
Abdominal wall	Abdominal wall transplantation (partial or full-thickness) was initiated in 2003. The indication is coverage of the fascia defect (when alternative techniques fail) after a life-saving intestinal and/or multi-visceral transplantation. Up to now, 38 full-thickness vascularised abdominal wall transplantations, 6 partial-thickness vascularised and 17 partial-thickness non-vascularised rectus fascia grafts have been performed [3] (see §7.2.4).
Femoral and knee joint – lower extremity	As in upper-extremity VCAs, the functional results of lower extremity transplantation depend on the level of amputation (proximal, mid- and distal femur or tibia), the more distal being associated with faster recovery and fewer complications. Currently the results of the 4 lower extremity transplants show limited outcomes [4-6].
Larynx and trachea	The indications for laryngeal transplantation are either 1. severe traumatic or stenotic injuries causing a loss of laryngeal function or 2. a large benign or low-grade malignant tumour, for which patients have undergone treatment by way of a total laryngectomy. At present, it is impossible to propose laryngeal transplantation to patients with locally advanced laryngeal cancer because immunosuppression is contraindicated. Tracheal replacement with prosthetic or biological substitutes such as allografts or autologous grafts (trachea, oesophagus, bowel, skin, bladder, aortic segment) is complex. The main critical issue is to manage allograft revascularisation [7-9].
Tongue	The putative indication for tongue transplantation, apart from face transplantation, could be cases of head and neck cancer with a functional deficit following total or subtotal loss of tongue tissue and graft-able hypoglossal and lingual nerves, in the absence of other contraindications. The first and only tongue transplantation was performed in 2003 [10].
Penis	Penile transplantation has been performed in five cases. Even if phalloplasty seems to be nowadays the best and efficient therapeutic option, some teams wish to develop such a VCA programme. Transgender people have expressed an interest in the procedure [11-12].

Sustained long-term physiotherapy is required to achieve functional recovery, which is also influenced by the level of amputation and the point of follow-up. All transplanted patients reached protective sensation, 91 % of them tactile sensation and 82 % a certain degree of discriminative sensation. Patients regained independence in daily activities, such as dressing, shaving, driving, riding motorcycles and writing, and some of them returned to work [15, 28].

15.2.1.2. *Face transplantation*

Face transplant (FT) candidates present with severe disfiguration involving functional 'aesthetic units', particularly those of the central part of the face (nose, upper and lower lips, chin and tongue). The functional deficits are correlated with the units involved: blindness, impaired or impossible swallowing, oral eating and drinking difficulty and slurred or unintelligible pronunciation. Many patients breathe through a tracheostomy and are fed via gastro- or jejuno-stomies [29-30]. Partial or total FT is considered when disfiguration affects more than two functional-aesthetic units of the face or scalp and when conventional plastic reconstructive surgery gives rise to poor results [31].

In the post-transplant phase, 72.7 % of face transplants have experienced one to nine episodes of skin AR (median 3) during a follow-up period ranging from 15 months to 10 years [15, 30]. Two cases of chronic rejection have been reported after FT [15, 22]. To the best of our knowledge, seven deaths among the face transplants have been declared to the registry since 2004 [30]. The IRHCTT reports a patient survival rate of 83.3 % at 10 years [15].

FT is aimed at improving the patients' QoL, based on both aesthetic and functional recovery, and 90 % of recipients declared an improvement in their QoL, although 50 % required medical treatment for complications [15]. Physical recovery is related to the need for further surgical enhancement after the transplant and to the progress of their functional status during the recovery phase (i.e. feeding, breathing). The capacity of the patient to integrate the graft into their body image also influenced their social re-integration [26]. Functional recovery has been assessed based on the recovery of discriminative sensibility, which was obtained in 90 % of recipients, and of muscular tone with consequent recovery of movements [15]. One year after transplantation, patients were able to perform the majority of basic movements and daily activities at various degrees, such as opening and closing eyelids, eating, drinking, swallowing, chewing, speaking, smiling, kissing and blowing [21].

The psychological situation is also complex as recipients have to deal with the distress of the disfiguration before the transplantation, and then the new body image and fear of the way others will perceive them [29, 32-33]. The psychological dimensions in FT are even more important than they are in UET. Candidates have severe facial disfigurement, with aesthetic and functional deficits, which may lead to depression, social isolation, alcohol abuse and increased risk of suicide in the majority of cases. The subjective patient's acceptance of the 'new' face and the patient's commitment to social reintegration are determinants for final transplantation success [34]. Unfortunately, psychological outcomes and QoL improvements that determine the value of the procedure are not well documented, and assessment protocols are needed to understand better whether the QoL improvement outweighs the actual risks of death derived from surgery and immunosuppression. Note that FT may not only improve the patient's QoL but also offers a new social identity [35-36]. At present, the international experience shows that FT is a valuable therapeutic option in properly selected candidates.

15.2.2. Recipient selection and informed consent

Candidates eligible for UET and FT are followed in reconstructive surgery centres and in rehabilitation centres. All amputees and severely disfigured patients are potential candidates for UET and FT, respectively, but only a few patients will be suitable for such transplantation. A careful evaluation and selection of the potential candidate is indispensable. Such transplantation requires a multidisciplinary approach for the evaluation and management of complex medical, psychiatric and social issues. Potential recipients have to be evaluated for reconstructive surgery and at the same time for transplantation. The psychosocial assessment is of utmost importance, due to past and current severe disabilities [21]. For UET, prosthetic management should be considered before transplantation decision. UET needs an intensive and long-lasting rehabilitation programme. Face transplant candidates should be thoroughly informed of all alternative surgical options for treating facial deformities or defects, but also of the psychological issues.

Patient motivation is indispensable throughout the long and slow rehabilitation period, which can last many months and sometimes years. In the follow-up, immunosuppressive therapy is mandatory. Acute and chronic rejection require further interventions. Patients' compliance with immunosuppres-

sive treatment and the rehabilitation programme is the key to achieving successful functional recovery. Establishing the patient's capacity to provide valid consent for VCA is a key element of the psychological evaluation. Since there is no possibility of establishing an objective risk-to-benefit ratio of allogeneic reconstruction, it is the ethical responsibility of the transplant team to provide comprehensive informed consent documentation for the patient to aid in the decision-making process.

Table 15.2. **Donor selection criteria: information for co-ordination centres**

Donor selection is based on the following criteria:
• Type of donor: DBD or DCD.
• Details of past trauma, maxillo-facial surgery; face cancer is a contraindication for face transplantation.
• Age range; gender; height and weight range; skin tone-phototype, hair pattern, tattoos.
• Blood group; HLA typing, prospective cross-match.
• Anthropometric criteria (main matching criteria):
– For upper extremities: photographs, level of amputation, upper extremity X-ray (anterior, posterior, lateral views) and measurements (length, circumferences), skin examination (no wounds/injuries), ultrasonography study of arteries (radial, cubital, palmar arches …) and veins (basilic cephalic). Note that radial catheter insertion has been responsible for graft thrombosis [23]. Preparation of the cosmetic prosthesis.
– For face: photographs, X-ray (anterior, posterior, lateral views) and measurements (specific to face segments), skin examination (no wounds/injury), computed tomography (with 3-dimensional reconstruction), angiography (to be discussed with the transplant team according to the nephrotoxicity); preparation of the facial mask.

15.2.3. Donor selection

The majority of grafts are procured from donation after the determination of death by neurologic criteria, i.e. brain death (DBD); grafts come less frequently from donation after circulatory death (DCD). Because of the limited number of candidates, all co-ordination teams involved in a VCA programme should be aware of any potential candidate, either already registered on an existing waiting list or otherwise proposed in the context of a clinical research protocol. For each proposed VCA recipient, previously validated by the Health Authority in charge of organ transplantation activities, the VCA surgical team or the protocol investigator should complete a standard technical sheet about each proposed donor, containing information on expected donor criteria (mainly morphologic criteria) for the best matching of donor and recipient (see Table 15.2). All other information should also be available, in order to facilitate donor detection and selection.

15.2.4. Consent to donation

The process of obtaining next-of-kin consent should obey the legal requirements in place nationally, whether the context is a clinical research programme or standard care. Currently the general public and relatives of potential donors are not, or may not be, aware of what VCAs are, or that they may be donated. In the USA, where VCA programmes have become standard care, once a matching donor is identified by the organ procurement organisation, a specific and explicit consent for VCA donation has to be obtained and documented through a separate consent process, independent of solid organ donation [37].

For hospitals not familiar with VCA procurement, support should be provided by the VCA centre in order to ensure that consent to VCA donation has been obtained properly and that all necessary questions have been asked. Best practice is that the person performing the VCA donation request is fully familiar with VCA procurement and transplantation, and trained to consider well all the issues that are briefly discussed in section 15.2.5.1.

15.2.5. Co-ordination teams

The lack of proactive detection of potential donors for VCA grafts might be associated with a negative perception of this type of transplantation and weak knowledge of the results. This underlines the need for dedicated co-ordinators, trained and confident in such communication during the interview with the relatives.

As a prerequisite, the co-ordination teams involved in VCA programmes should be part of such a programme on a voluntary basis, being already involved in DBD/DCD procurement activity. They should be aware of the potential recipients on the waiting list and, for each of them, their donor profile; all of this information should be known by the procurement centres, on the basis of the technical sheet describing the donor selection criteria (see Table 15.2). As soon as a potential VCA donor is identified by the co-ordination team, the Health Authority in charge of organ allocation must be rapidly informed of such potential procurement in order to begin searching for the best match among the potential recipient(s) on the waiting list, in conjunction with the VCA (and solid organ) transplant teams involved. Currently, VCA donors in Europe are mostly detected and allocated locally, in accordance with the morphologic

characteristic-matching required with the potential candidate.

The VCA centre's co-ordination team should help any hospital unfamiliar with VCA procurement to organise and prepare for it. See box below.

15.2.5.1. *Interview*

Requesting part of a limb or a face is different from requesting a life-saving organ such as a heart, because they are visible, external and highly sensitive body parts where removal may naturally provoke reluctance in the family. At present, co-ordinators begin and secure the interview by presenting the opportunity of solid organ donation before any other approach. The most desired situation would be when, following the co-ordinator's request for a VCA donation, the relatives spontaneously suggest that the potential donor 'wanted to donate every organ' and they show that they are definitely open-minded about VCA donation.

In cases of donation acceptance, co-ordinators should be able to give appropriate information to the relatives on VCA activities, the procurement modalities and post-transplantation outcomes (global aesthetic and functional results). Since an osseous and cartilaginous substructure defines the face shape, the recipient's face will look different from the donor's face, unlike hand- or upper extremity transplants. Co-ordinators should stress that face donation will allow the restoration firstly of basic functions such as breathing, swallowing, eating, drinking and speaking, and only secondarily an 'acceptable' appearance. For upper extremity transplantation, because the donor's personal traits will be more visible, the physical matching criteria (limb size and length, skin and pilosity, gender) are more relevant in donor selection.

The possibility of procuring supplementary material such as haematopoietic stem cells, skin or bone tissue should also be explained. Intended for the immunosuppressive strategy and/or further surgery, they are best procured from the unused parts of the grafts.

The obligation to give back to the relatives the deceased body consistent with the original image is a key point in any successful VCA programme in order to maintain a climate of absolute trust, as much for the next-of-kin's sake as for the sake of the medical community. It is essential to tell the relatives about the policy and practice of *ad integrum* body restitution – restoration of the donor's external appearance and physical integrity using cosmetic prosthesis – and it is important to recall this fact during the interview.

The co-ordinator should inform the donor family that, despite all efforts and the obligation of professional discretion in all circumstances, protection of confidentiality cannot always be respected as it should be. Transplanted patients usually accept requests to be shown in public or scientific meetings, which might unintentionally compromise the donor's anonymity.

15.2.5.2. *Procurement*

The co-ordinator's role in the operating room is essential, to manage the temporal and logistical constraints of simultaneous multi-organ procurement, with management of the different teams (e.g., novice plastic surgeons with experienced organ teams). They should be aware of the planned sequence of VCA/organ retrieval to guarantee a well co-ordinated process and, when required, to accelerate the solid organ procurement. For face procurement, the co-ordination team should be reinforced due to the surgery time.

> The VCA centre's co-ordination team – and the centre's procurement team – must provide on-site support and a clearly defined checklist to any hospital not familiar with VCA procurement. Checklists should cover every step of the entire procedure. Both teams should fully respect the fact that teams in such hospitals are not familiar with the procedure and will need *ad hoc* training, explanation and appropriate guidance as a prerequisite. After the procurement is completed, a debrief session by the VCA team is mandatory.

15.2.5.3. *Specific training*

According to Directive 2010/53/EU [13], specific training programmes should be developed, but to date there are no existing international standards or guidelines. The success of VCA programmes mainly depends on surgeons' willingness to regularly interact with the co-ordination centres. The more the surgeons are involved and informed about the demand for and progress in VCA, the better they will promote this activity and approach the donors' relatives with confidence.

If hospital co-ordination and donation teams are not affiliated to a VCA centre, they are probably not familiar with the details of any kind of VCA. In a VCA centre it is very likely that a dedicated core team is familiar with the kind of VCA performed in that centre. Based on these assumptions, an education programme will have to be developed, with appropriate guidance from the VCA core team, to enable co-ordination and donation teams to manage a VCA donation procedure without harm to any of those concerned, including other interests in the healthcare system. Although the VCA centre's core team may

have been preparing the donation–transplantation procedure for a long time in advance, we must be aware that other co-ordination and donation teams may have a severe 'psychological shock' if they are suddenly exposed to this issue for the first time.

15.2.6. VCA procurement

15.2.6.1. *VCA procurement sequence*

As a rule, multi-organ procurement should not be compromised by VCA retrieval. No case of solid-organ transplantation being compromised by VCA retrieval has been reported. Up to now, no standardised protocol for VCA procurement has been established, but experience is well described [38-40]. More than two thirds of limb and face procurement started with VCA recovery, followed by the multi-organ procurement simultaneously or immediately after VCA retrieval. The outcome of solid organ transplants does not seem to be affected [31]. Actually, donor haemodynamic stability is the critical factor determining the optimal timing of VCA retrieval. Because of the added complexity of VCA retrieval alongside the multi-organ procurement procedure, a detailed algorithm for each individual case, planning each team's function and intervention order, is required before the day of such events occurs. Positions for face/limb, thoracic and abdominal teams working simultaneously should be described in a schema depicting operating-room arrangements [39-40]. Communication between all procurement teams is essential, before and during surgery, to ensure efficient and safe retrieval with the best viability of all organs.

15.2.6.2. *VCA recovery phase*

15.2.6.2.1. Upper extremities

For upper extremities, the most important criterion in matching donor and recipient is the limb size. This is a straightforward and rapid recovery procedure, with minimal blood loss and minimal risk of destabilising the donor's haemodynamic conditions. Mean duration is 1 hour. Amputation under a tourniquet is performed just before solid-organ recovery; the graft is perfused on the back table with pre-defined preservation solution. In a few cases, VCA recovery has been performed after vital organ procurement, mostly because this was forced by the donor's haemodynamic instability. When possible, a preservation technique using specific cannulation of proximal vessels (i.e. brachio-cephalic or sub-clavian) while keeping the venous return may improve the upper extremity viability (and is recommended in the case of an unstable donor). Upper extremities are prepared for transplantation and kept in ice pack while the VCA recipient is prepared. The graft is packed in dry and cold labelled bags and transported in an isotherm container. During the body restoration, the custom-made cosmetic prostheses are put in place.

15.2.6.2.2. Face

The duration of facial segment recovery is highly variable (4 to 15 hours); this is a function of the recovery sequence (sequential or simultaneous) and the number and type of aesthetic units to be replaced and consequently to be retrieved. The procedure's complexity can induce blood loss in volume and compromise circulatory control. On the basis of the experience of face procurement in DBD, tracheostomy (preferred to tracheal tube) and a mould for the facial mask could be performed pre-operatively in the ICU [40]. Usually, organ recovery starts with heart and lungs, along with liver, pancreas and small intestine. Kidneys and face are then removed. In some cases, donor haematopoietic cells have been simultaneously collected by a bone marrow aspirate from the iliac crest in order to induce a chimerism-tolerance status. Skin from the donor should be retrieved, at best issued from unused parts of the graft, to be further frozen. Donor bone tissue retrieved from an unused part of the graft is sent to the tissue bank. Facial graft is prepared on the back table, washed and packed in dry, cold and labelled bags for transportation in an isotherm container.

15.2.6.2.3. Restoration

Body restoration is a usual and mandatory step in any organ/tissue procurement, but of the utmost importance in any case. Replacement of the extremities or the face should be done using well-designed prostheses and mask, ensuring a perfectly restored external appearance.

15.2.6.2.4. Times

Since most VCA procurements have been performed locally, ischaemia times are around 4 hours [38, 40]. Median cold ischaemia time was around 356 minutes (30-365) in upper extremity transplantation and 132 minutes (20-540) in face transplantation [25, 41]. Although no current clinical studies exist, time minimisation is advocated. As surgical procedures expand to include an increasing number of potential

recipients, the effect of the ischaemic time becomes more important [38, 42].

15.3. Special issues in donation of grafts for uterus transplantation

15.3.1. Uterus transplantation: a rapidly expanding activity

Uterus transplantation (UTx) has become since 2014 an alternative to adoption or gestational surrogacy, indicated for women suffering from absolute uterine factor infertility (AUFI). Among the different existing options of reproductive medicine strategies, it offers the possibility of an entire genetic and gestational motherhood. The origin of AUFI could be congenital, mostly represented by Mayer–Rokitansky–Küster–Hauser syndrome (MRKH) or acquired after hysterectomy (cancer, benign disease etc.). So far, the majority of UTx indications have been represented by MRKH (Müllerian aplasia).

To date, over 70 UTx procedures have been performed all over the world, resulting in over 20 live births according to the update from the International Society of Uterus Transplantation (ISTUx) annual meeting (September 2019, Cleveland, USA), compared to 52 UTx reported at Ghent in October 2018 [43]. Fewer than half of these cases have been published in the scientific literature [44]. The first study of a series of 9 UTx was initiated in 2012 in Gothenburg, Sweden [45]. The first live birth occurred in 2014 [46], launching a rapidly extending field. The first series of UTx was performed with living donors, as in the majority of all other cases worldwide (Saudi Arabia, USA, China, Germany, Serbia, Czech, India, France). The first live birth from a transplanted uterus issued from a deceased donor was reported in Brazil in 2017 [47]. The take-home baby rate has not yet been revealed, due to the relative short follow-up time in most of the performed cases, but it may be over 80 % in experienced centres, according to unpublished data presented at the annual meeting.

All the pregnancies require IVF procedure surrounded by medically assisted reproduction and gametes regulation. The optimal time for the initial embryo transfer is still debatable (6 to 18 months), with a majority of live births after embryo transfer at 12 months [48]. Early graft failures have been reported in all of the larger case series performed so far, mainly due to vascular complications [44]. After the birth of one to two healthy babies or failure to achieve this within a limited time period, the uterus is removed and the immunosuppression discontinued. The uterus is thus the only organ to be transplanted temporarily, unless it is donated from a monozygotic twin as in the case from Belgrade. Some authors have evoked the possibility of uterus domino transplantation [49].

General ethical principles in cases of living donation are developed in Chapter 13. Surveys of public attitudes performed in the UK, Japan and the USA concluded that there was public acceptance of UTx, with a positive attitude. In cases of infertility, women would rather choose UTx than adoption or gestational surrogacy [50-51]. Besides, specific ethical issues concern the surgical risks for the living donor (hysterectomy) and for the recipient (transplantation, delivery caesarean, hysterectomy). Long-term effects of immunosuppression exposure (even if the exposure is temporary) should be determined by long-term and regular follow-up of these children.

Historically, UTx has fallen under VCA legislation, considered as a non-vital organ and still experimental although, from a technical point of view, it is very similar in that uterus retrieval is performed as with other abdominal solid organs and the transplantation relies upon vascular anastomosis and venous outflow, a key step common to solid organ transplantation. Like other VCAs, UTx needs a multidisciplinary framework, particularly in this case because it mixes transplantation surgery and gynaecologic care, together with assisted reproduction activities, with their own legal framework to be clarified by the national Health Authority in the near future. Like UE or face transplantation activities, UTx is mostly still performed under clinical research protocols worldwide. Based on a solid learning curve (successful procedures, rigorous protocols including long-term follow-up of the living donor and the children), Swedish and American teams will next proceed to UTx as standard of care. We must keep in mind that the success of UTx launching by the Brännström team in Sweden came after more than 10 years of animal-based research, underlining the specific surgical skills to overcome [49, 52].

15.3.2. Living donors

15.3.2.1. *Donor selection criteria*

Living donation, as a planned procedure, allows exhaustive screening of the uterus viability and pregnancy potential, vasculature and premalignancy conditions, when compared to deceased donation with its time constraints.

The donor should have completed her own family formation. With the exception of the Dallas

trial, where the majority were altruistic donors [53], donors have been related – either genetically or as friends. Altruistic donors should only be accepted in experienced centres until we have further knowledge of the complication rate. Due to the atrophy of the uterus and the uterine arteries, the donor should not have been menopausal for several years as this may affect the outcome, as we have learned from the early cases. In cases of menopause, the donor has to be on hormone replacement therapy in order to evaluate the endometrium. The donor should be assessed as being of good health according to national guidelines of living donor investigations, including expanded screening for risks of thrombosis due to the prolonged donor surgery [44]. A fully gynaecologic assessment of the history of pregnancies, partum and gynaecologic health, including screening for cervical dysplasia and an investigation of the uterus and its vascular supply, has to be performed. Imaging of the vasculature is of utmost importance [54].

15.3.2.2. *Consent to donation*

Fully informed consent has to be obtained, according to existing ethical guidelines and legislation for living donation, including consent to research protocol (refer to Chapter 13). The multidisciplinary team should also include a social worker and a psychologist for a rigorous evaluation of the living donor and of the recipient hoping to achieve pregnancy. They must be aware of the surgical risks, their potential complications, the immunosuppressive therapy and their own risks, and the risk of failure all along the process until the expected livebirth.

15.3.2.3. *Uterus procurement: follow-up*

Uterus procurement (hysterectomy) in the living donor has been realised by an open laparotomy approach with an initial duration time of 10 to 13 hours, mainly due to the fragile dissection of the deep vessels from the ureter proximity. With improved practice, the duration time has fallen to 5-7 hours, but now a new approach (robotic-assisted laparoscopy) is proposed to further reduce the duration of the hysterectomy and possibly the blood loss (less than one litre in median) [55-56]. The donors should be followed up for a minimum of one year in order to discover any late complications related to the complex surgery. It is especially important to identify delayed manifestation of ureter injury because this may affect the kidneys. Due to the novelty of the procedure, a lifelong follow-up should be put in place, as for all living donors (refer to Chapter 13). The follow-up should include sonography of the kidneys, lab testing, clinical evaluation and counselling in case of psychosocial issues.

15.3.3. Deceased donor

15.3.3.1. *Donor selection criteria*

To date, only two livebirths after a UTx issued from a deceased donor have been reported, in Brazil and USA (Cleveland), after several attempts since the first one performed in Türkiye in 2011 [57]. Details of other successful live births, which occurred more recently, are to be published [58]. In this situation of deceased donation, the donor selection criteria have not been fully explored. High-risk donors (e.g. ≤ 60-year old woman and menopausal) should not be accepted as it is not a lifesaving procedure. DCD donors have not until now been accepted.

Donor-selection criteria on donor age differ between centres, between nulliparity and multiparity. For the Swedish team, the ideal donor is within the living donor criteria but the age has to be below the upper limit of a living donor to avoid the risk of prolonged menopause. The maximal donor age was 45 years old [47, 58]. Successful UTx has been performed from a deceased nulliparous woman in Prague. The minimal screening should include an evaluation of sexual behaviour, HPV status and ultra-sonography (or other imaging) of the uterus. Some authors recommend a colposcopy during the retrieval (and even an hysteroscopy *ex vivo*) of the uterus to discard any potential cervical dysplasia or polyp [58-59].

Table 15.3. **Specific inclusion criteria for uterus donation after DBD [59]**

Age (y): 18-45
No history of malignancies (including endometrial dysplasia)
No major abdominal or pelvic surgery (including caesarean section or abortion)
Normal Pap smear (when available)
No active infection and negative for: gonorrhoea, chlamydia, syphilis, HIV, HBV, HCV
Negative human papillomavirus (HPV) status or previously vaccinated for HPV
No history of drugs or alcohol abuse; safe sexual behaviour
Normal uterus morphology or blood supply on ultrasonography or other imaging

15.3.3.2. *Consent to donation*

As with other organs, the consent should be in accordance with national legislation on organ donation (refer to Chapter 4), including a specific consent for donation of the uterus, separate from the consent for donation of other organs. In some countries, this

will be seen within the context of consent to clinical research if uterus transplantation is not considered part of the field of organ transplantation along with VCAs.

15.3.3.3. *Uterus procurement*

The uterus procurement is planned to fit with the timing of the retrieval of the other abdominal organs. The uterus has to be flushed with organ preservation fluid, like the rest of the abdominal organs. Hence the cannulation has to allow flushing of the internal iliac arteries bilaterally. Different techniques have been developed for removing the organ both before and after the other solid organs. In the two successful cases, the other organs have been removed before the uterus retrieval. Some authors consider the uterus as a solid pelvic organ, to be ideally retrieved first before aortic clamping. There have not been any reports of injury to the other vital organs procured from the multiorgan donor due to the uterus retrieval. The procedure takes 1 to 2 hours, and the vessel dissection is easier than in a living donor, mainly for the vessel separation from the distal ureters.

First of all, the precise sequence of uterus procurement (timing of aortic clamping, timing for each of the solid organs to be retrieved) has to be communicated to all the teams involved, before the procurement by the co-ordination team [59]. According to animal research, the uterus can sustain a prolonged period (up to 24 hours) of ischaemia [60]. The ischaemia time of the first successful reported case was 8 hours, with cold and warm ischaemia times of 380 minutes and 90 minutes respectively [47]. Protocols should precisely define and detail what are the different ischaemia times (warm and cold), both in living and deceased donation [61].

15.4. Conclusion

In summary, initial outcomes based on the few preliminary data are in favour of upper extremity, face and uterus transplantation feasibility. The shift from innovative therapy to standard care status should be thought through with caution. For uterus transplantation, the transition from experimental care to standard care is greatly expected by many professionals. The key of the success of UET and FT relies upon pro*per se*lection of the recipient and a well-established, interdisciplinary, comprehensive approach to the field in specialised transplant centres. Besides the need for complementary, collaborative outcomes, data and transparency, as well as standardised and shared protocols, clinical research is focusing on different strategies to mitigate the heavy burden of the immunosuppression.

Uterus transplantation activity has rapidly progressed worldwide, with a new challenge in deceased donation. However, due to the limited number of VCA transplants performed up to now, two issues need to be considered:

a. Further data are required to demonstrate the long-term benefits of each single VCA for the recipient, as well as the cost for society.

b. Training of healthcare professionals – especially people involved in organ donation – is needed on how to manage VCA donations well without harm to other issues of organ and tissue donation.

Research agenda

From the literature and discussion of the available evidence, several topics have been identified for which evidence is inconsistent, insufficient or non-existent. The authors of this guide recommend that future research, where possible in well-designed randomised clinical trials, should focus on the following research gaps:

1 Best approach for UTx between living or deceased donor.
2 Long-term consequences of immunosuppressive treatment on both the mother and her baby.

15.5. References

1. Dubernard JM, Owen E, Herzberg G *et al.* Human hand allograft: report on first 6 months. *Lancet* 1999; 353:1315-20.
2. Devauchelle B, Badet L, Lengele B *et al.* First human face allograft: early report. *Lancet* 2006;368:203-9.
3. Giele H, Vaidya A, Reddy S *et al.* Current state of abdominal wall transplantation. *Curr Opin Organ Transplant* 2016;21:159-64.
4. Kirschner MH, Brauns L, Gonschorek O *et al.* Vascularized knee joint transplantation in man: the first two years experience. *Eur J Surg* 2000;166:320-7.
5. Zuker RM, Redett R, Alman B *et al.* First successful lower-extremity transplantation: technique and functional result. *J Reconstr Microsurg* 2006;22:239-44.
6. Cavadas PC, Thione A, Blanes M, Mayordomo-Aranda E. Primary central nervous system post-transplant lymphoproliferative disease in a bilateral transfemoral lower extremity transplantation recipient. *Am J Transplant* 2015;15:2758-61.
7. Knott PD, Hicks D, Braun W, Strome M. A 12-year perspective on the world's first total laryngeal transplant. *Transplantation* 2011;91:804-5.
8. Delaere P, Vranckx JJ, Meulemans J *et al.* Learning

curve in tracheal allotransplantation. *Am J Transplant* 2012;12:2538-45.

9. Macchiarini P, Jungebluth P, Go T *et al.* Clinical transplantation of a tissue-engineered airway. *Lancet* 2008;372:2023-30.
10. Chi JJ, Haughey BH. Tongue transplantation. *Curr Otorhinolaryngol Rep* 2014;2:178-83.
11. Tuffaha SH, Damon S. Cooney DS *et al.* Penile transplantation: an emerging option for genitourinary reconstruction. *Transpl Int* 2017;30:441-50.
12. Szafran AA, Redett R, Burnett AL. Penile transplantation: the US experience and institutional program set-up. *Transl Androl Urol* 2018;7:639-45.
13. European Parliament and Council of the European Union: Directive 2010/53/EU of the European Parliament and of the Council of 7 July 2010 on standards of quality and safety of human organs intended for transplantation. 2010. *Official Journal of the European Union* 2010;53:14-29.
14. OPTN (Organ Procurement and Transplantation Network). A proposed rule by the Health and Human Services Department on 12/16/2011. *Federal Register* 2011;76(242), available at www.federalregister.gov/documents/2011/12/16/2011-32204/organ-procurement-and-transplantation-network, accessed 19 July 2021.
15. International Registry on Hand and Composite Tissue Transplantation (IRHCTT), available at www.handregistry.com, accessed 19 July 2021.
16. Petruzzo P, Sardu C, Lanzetta M and Dubernard JM. Report (2017) of the International Registry on Hand and Composite Tissue Allotransplantation (IRHCTT). *Curr Transplant Reports* 2017;4(4):294-303.
17. Cavadas PC, Landin L, Thione A *et al.* The Spanish experience with hand, forearm, and arm transplantation. *Hand Clin* 2011;27:443.
18. Landin L, Bonastre J, Casado-Sanchez C *et al.* Outcomes with respect to disabilities of the upper limb after hand allograft transplantation: a systematic review. *Transpl Int* 2012 Apr;25(4):424-32.
19. Honeyman C, Fries CA. Vascularised composite allotransplantation – basic science and clinical applications. *International Journal of Orthoplastic Surgery* 2019 Jan:2;13-22. https://doi.org/10.29337/ijops.28.
20. Petruzzo P, Gazarian A, Kanitakis J *et al.* Outcomes after bilateral hand allotransplantation: a risk/benefit ratio analysis. *Ann Surg* 2015 Jan;261(1):213-20.
21. Jowsey-Gregoire SG, Kumnig M, Morelon E *et al.* The Chauvet 2014 Meeting Report: Psychiatric and psychosocial evaluation and outcomes of upper extremity grafted patients. *Transplantation* 2016;100(7):1453-9.
22. Morelon M, Petruzzo P, Kanitakis J. Chronic rejection in vascularized composite allotransplantation. *Curr Opin Organ Transplant* 2018:23;582-91.
23. Kanitakis J, Petruzzo P, Badet L *et al.* Chronic rejection in human vascularized composite allotransplantation (hand and face recipients): an update. *Transplantation* 2016;100(10):2053-61.
24. Schneeberger S, Gorantla VS, van Riet RP *et al.* Atypical acute rejection after hand transplantation. *Am J Transplant* 2008 Mar;8(3):688-96.
25. Petruzzo P, Lanzetta M, Dubernard JM *et al.* The International Registry on Hand and Composite Tissue Transplantation. *Transplantation* 2010;90:1590-4.
26. Lantieri L, Grimbert P, Ortonne N *et al.* Face transplant: long-term follow-up and results of a prospective open study. *Lancet* 2016 Oct 1;388(10052):1398-1407.
27. Nasir S, Kilic YA, Karaaltin MV, Erdem Y. Lessons learned from the first quadruple extremity transplantation in the world. *Ann Plast Surg* 2014 Sep;73(3):336-40.
28. Shores JT, Malek V, Andrew Lee WP, Brandacher G. Outcomes after hand and upper extremity transplantation. *J Mater Sci Mater Med* 2017 May;28(5):72.
29. Sosin M, Rodriguez ED. The face transplantation update: 2016. *Plast Reconstr Surg* 2016 Jun;137(6):1841-50.
30. Cavadas PC, Landin L, Ibañez J *et al.* The Spanish experience with face transplantation. In: Siemionow MZ, ed. *The know-how of face transplantation*. London: Springer 2011:351-61.
31. Siemionow MZ, Papay F, Djohan R *et al.* First U.S. near-total human face transplantation: a paradigm shift for massive complex injuries. *Plast Reconstr Surg* 2010 Jan;125(1):111-22.
32. Khalifian S, Brazio PS, Mohan R *et al.* Facial transplantation: the first 9 years. *Lancet* 2014 Dec 13;384(9960):2153-63.
33. Westvik TS, Dermietzel A, Pomahac B. Facial restoration by transplantation: the Brigham and Women's face transplant experience. *Ann Plast Surg* 2015 May;74(Suppl 1):S2-S8.
34. Coffman KL, Siemionow MZ. Face transplantation: psychological outcomes at three-year follow-up. *Psychosomatics* 2013 Jul-Aug;54(4):372-8.
35. Aycart MA, Kiwanuka H, Krezdorn N *et al.* Quality of life after face transplantation: outcomes, assessment tools, and future directions. *Plast Reconstr Surg* 2017 Jan;139(1):194-203.
36. Fischer S, Kueckelhaus M, Pauzenberger R *et al.* Functional outcomes of face transplantation. *Am J Transplant* 2015 Jan;15(1):220-33.
37. OPTN (Organ Procurement and Transplantation Network). OPO guidance on VCA deceased donor authorization, available at https://optn.transplant.hrsa.gov/resources/guidance/opo-guidance-on-vca-deceased-donor-authorization, accessed 19 July 2021.
38. Schneeberger S, Morelon E, Landin L; ESOT CTA

Committee. Vascularised composite allotransplantation: a member of the transplant family? *Transplantation* 2012 Jun 15;93(11):1088-91.

39. Datta N, Yersiz H, Kaldas F, Azari K. Procurement strategies for combined multiorgan and composite tissues for transplantation. *Curr Opin Organ Transplant* 2015 Apr;20(2):121-6.
40. Brazio PS, Barth RN, Bojovic B *et al.* Algorithm for total face and multiorgan procurement from a brain-dead donor. *Am J Transplant* 2013 Oct;13(10):2743-9.
41. Aycart MA, Alhefzi M, Sharma G *et al.* Outcomes of solid organ transplants after simultaneous solid organ and vascularized composite allograft procurements: a nationwide analysis. *Transplantation* 2017;101:1381-6.
42. Hausien O, Swanson EW, Abraham JA *et al.* Surgical and logistical aspect of donor limb procurement in hand and upper extremity transplantation. *Vascularised Composite Allotransplantation* 2014;1:31-41.
43. Tummers P, Göker M, Dahm-Kahler P *et al.* Meeting report: first state-of-the-art meeting on uterus transplantation. *Transplantation* 2019;103:455-8.
44. Brännström M, Enskog A, Kvarnström N *et al.* Global results of human uterus transplantation and strategies for pre-transplantation screening of donors. *Fertil Steril* 2019;112:3-10.
45. Brännström M, Johannesson L, Dahm-Kähler P *et al.* First clinical uterus transplantation trial: a six-month report. *Fertil Steril* 2014;101:1228-36.
46. Brännström M, Johannesson L, Bokström H *et al.* Livebirth after uterus transplantation. *Lancet* 2015; 385:607-16.
47. Ejzenberg D, Andraus W, Mendes LRBC *et al.* Live-birth after uterus transplantation from a deceased donor in a recipient with uterine infertility. *Lancet* 2018;392:2697-2704.
48. Brännström M. Current status and future direction of uterus transplantation. *Curr Opin Organ Transplant* 2018; 23:592-7.
49. Brännström M, Dahm Kähler P, Greite R *et al.* Uterus transplantation: a rapidly expanding field. *Transplantation* 2018:102;569-77.
50. Hariton E, Bortoletto P, Goldman RH *et al.* A survey of public opinion in the United States regarding uterine transplantation. *J Minim Invasive Gynecol* 2018;25:980-5.
51. Kisu I, Banno K, Soeda E *et al.* Survey of attitudes toward uterus transplantation among Japanese women of reproductive age: a cross-sectional study. *PLoS ONE* 2016;11(5):e0156179.
52. American Society for Reproductive Medicine position statement on uterus transplantation: a committee opinion. *Fertil Steril* 2018;110:605-10.
53. Testa G, Koon E, Johannesson L *et al.* Living donor uterus transplantation: a single center's observations and lessons learned from early setbacks to technical success. *Am J Transplant* 2017;17:2901-10.
54. Mahmood S, Johannesson L, Testa G, de Prisco G. DUETS (Dallas UtErus Transplant Study): The role of imaging in uterus transplantation. *SAGE Open Med* 2019;7:2050312119875607.
55. Brännström M, Dahm-Kähler P, Kvarnström N *et al.* Live birth after robotic-assisted live donor uterus transplantation. *Acta Obstet Gynecol Scand* 2020 Sep;99(9):1222-9. https://doi.org/10.1111/aogs.13853. PubMed PMID: 32196630.
56. Johannesson L, Koon EC, Bayer J *et al.* Dallas UtErus Transplant Study: early outcomes and complications of robot-assisted hysterectomy for living uterus donors. *Transplantation* 2021 Jan 1;105(1):225-30. https://doi.org/10.1097/TP.0000000000003211. PubMed PMID: 32150040.
57. Akar ME, Ozkan O, Aydinuraz B *et al.* Clinical pregnancy after uterus transplantation. *Fertil Steril* 2013; 100:1358-63.
58. Kristek J, Johannesson L, Testa G *et al.* Limited availability of deceased uterus donors: a transatlantic perspective. *Transplantation* 2019;103:2449-52.
59. Chmel R, Pastor Z, Novackova M *et al.* Clinical pregnancy after deceased donor uterus transplantation: lessons learned and future perspectives. *J Obstet Gynaecol Res* 2019;45:1458-65.
60. Tricard J, Ponsonnard S, Tholance Y *et al.* Uterus tolerance to extended cold ischemic storage after auto-transplantation in ewes. *Eur J Obstet Gynecol Reprod Biol* 2017;214:162-7.
61. Tardieu A, Dion L, Lavoué V *et al.* The key role of warm and cold ischemia in uterus transplantation: a review. *J Clin Med* 2019 May 29;8(6):760.

Chapter 16. **Biovigilance and surveillance**

16.1. Introduction

Biovigilance is a framework for the detection, collection and analysis of information on unexpected and untoward occurrences associated with the use of medical products of human origin (MPHO). Vigilance and surveillance (V&S) applied to MPHO are essential components of this overarching system through which adverse occurrences are monitored to enable implementation of preventive and corrective measures.

The development of a vigilance system applied to organ donation and transplantation is in fact a requirement of Organ Directive 2010/53/EU of the European Parliament and of the Council on standards of quality and safety of human organs intended for transplantation [1].

Professionals involved in all aspects of organ donation and transplantation ought to be familiar with the concept of biovigilance and its practical applications, because they have the responsibility to recognise and monitor harm and the risk of harm to patients; we all have a duty to report such occurrences, contribute to investigations, implement necessary changes and promote dissemination of information to improve practice.

This chapter outlines the essential elements of an efficient biovigilance programme and gives a step-by-step description of how to deal with incidents in a systematic and didactic manner.

In summary, the aim of this chapter is to give a practical overview of this important topic in a manner that brings healthcare professionals, managers and health authorities together, to deliver a common goal of continuously improving the quality of processes, safety and outcomes for donors, donor families and recipients of transplanted organs.

16.2. V&S terminology and examples

The terms 'biovigilance' and 'vigilance and surveillance' (V&S) will be used interchangeably in this chapter. As with any other internationally used system, there exists a set of pre-determined terms that are commonly used in V&S. Their use facilitates harmonisation of practice between establishments and comparison of trends across different V&S systems. For details, readers should consult the report from the European Framework for the Evaluation of Organs for Transplant (Efretos) [2]. It is acknowledged that the application of rigid terminology is not always straightforward in practice and that a level of local interpretation may be applied. Professionals reporting incidents are not usually responsible for classifying them, so in-depth knowledge of quality system definitions is not necessary; however, familiarity with such common terminology can help with the identification of untoward events and is therefore encouraged.

Classifying what type of occurrence constitutes an 'event' or a 'reaction' – and whether or not they are of a serious nature – is often used to instruct professionals on the need to report adverse occurrences; it is also used to define whether or not the Biovigilance office needs to inform the health au-

thority (HA) about the occurrence and how the incident should be handled. In practice, however, a clear classification may not always be apparent right from the outset. It is important therefore to remember that incidents should be systematically recognised and promptly reported; inability to classify the type of occurrence should never delay or prevent reporting. With these important concepts in mind, some terms classically used in biovigilance are hereby defined for ease of reference.

16.2.1. Serious Adverse Event

The term Serious Adverse Event (SAE) refers to any undesired and unexpected occurrence associated with any stage of the chain from donation to transplantation that has not yet caused harm but has the potential to do so. Directive 2010/53/EU specifically defines an SAE as an 'occurrence that has the potential to lead to the transmission of a communicable disease, to death or life-threatening, disabling or incapacitating conditions for patients or which might result in, or prolong, hospitalisation or morbidity' [1]. An SAE also includes what is commonly referred to as a 'near miss', to indicate an error or fault that is detected and corrected without causing harm, but where there was the potential of causing serious harm to a living donor or to an organ recipient.

16.2.2. Serious Adverse Reaction

The term Serious Adverse Reaction (SAR) refers to an occurrence that has resulted in actual harm to a living donor or to an organ recipient. Directive 2010/53/EU defines an SAR as "an unintended response in a living donor or transplant recipient that might be associated with any stage of the chain from donation to transplantation that has caused fatal, life-threatening, disabling, incapacitating harm or which has resulted in, or has prolonged hospitalisation or morbidity" [1].

16.2.3. Adverse occurrence

A non-serious adverse occurrence can be an event or reaction leading to minor or nil impact on living donors or recipients. Adverse events (AEs) usually result from minor deviations from standard operating procedures and protocols. Adverse reactions (ARs) relate to clinical complications that are minimal in nature and easily managed and resolved. Incidents initially perceived to be minor may evolve into SAREs if not identified and rectified. Equally, the distinction between serious and non-serious occurrences may not be apparent from the outset; therefore prompt and appropriate reporting must always take place, unless it is very clear that the occurrence can be safely managed within local quality management systems (Chapter 17).

Examples of serious adverse events and reactions (SAREs) can be found in Table 16.1. They are listed for illustrative purposes and, as previously mentioned, a slight variation in classification may be applied in different countries or regions, according to local protocols. Ultimately, provided there are mechanisms to deal with such incidents appropriately, measures will be taken to address all relevant issues.

16.2.4. Vigilance and surveillance

In the context of organ transplantation, V&S is a system for the monitoring of adverse occurrences, which must lead to preventive and corrective measures to avoid SAREs, thus protecting the health of organ recipients and living donors.

Routine monitoring of clinical outcomes is an integral part of the surveillance system. Clinical teams set up registries, with follow-up on graft function and recipient outcomes as well as living-donor outcomes, in order to monitor trends and to identify new safety risks. For example, surveillance of SAREs can reveal systemic causes for recurrence and frequency of adverse occurrences, allowing targeted intervention.

16.2.4.1. *Surveillance for new risks (horizon scanning)*

Horizon scanning for potential and emerging threats to the safety of MPHOs is an integral part of risk surveillance. It is done through a systematic examination of information and should include early warning of new risks (risk identification and monitoring), management of the evolving epidemiological situation (risk management) and communication processes to relevant stakeholders (risk communication) [3].

Newly emerging or re-emerging infectious diseases, for example, can be identified through monitoring of trends (risk identification); management of such risk may include targeted testing or individual risk-based assessment of donors and recipients. New risks may also be related to new techniques, new medical devices or new reagents used at any stage of the donation and transplantation process.

The European Centre for Disease Control (ECDC) monitors the epidemiology of diseases in Europe and publishes a weekly *Eurosurveillance* report that provides useful data to inform donor selection. The ECDC also performs risk assessments

of particular epidemic agents and other infectious diseases, publishing Rapid Risk Assessments/reports as and when required (see www.ecdc.europa.eu/en/threats-and-outbreaks/reports-and-data/risk-assessments).

Table 16.1. **V&S examples**

A. Examples of adverse events (AEs)

Occurrence	*Organs*	*Case description and impact*	*AE type*
Organ packaging error	Kidney	Mix-up of organs in the transport box; right kidney *versus* left kidney. Vascular anatomy mismatch at surgery but surgical adjustment made	Mix-up → Incorrect MPHO applied → Risk of harm → No harm
Communication of incorrect donor screening result	Multivisceral-cardiothoracic and abdominal organ donation	Incorrect donor microbiology result communicated verbally to the OPO co-ordinator. Error identified and corrected promptly by transmitting a hard copy of laboratory report with correct results	Deviation from process → Risk of harm → No harm
Contamination of organ preservation fluid	Kidney, pancreas and liver	Surface contamination of organs with donor gastrointestinal microbiota during abdominal multi-organ recovery; fully sensitive *E. coli* isolated. Recipients did not require change in management and did not develop any infectious complications peri-operatively	No deviation from process → Risk of harm → No harm

B. Examples of serious adverse events (SAEs)

Occurrence	*Organs*	*Case description and impact*	*SAE type*
Fungal contamination of organ preservation fluid	Kidneys and pancreas	*Candida albicans* isolated from organ preservation fluid following abdominal multi-organ recovery. Management of recipients varies between centres and may involve antifungal prophylaxis and/or close follow-up for signs of complications (mycotic aneurysm of renal artery)	No deviation from process → Risk of harm to recipient → SAE (SAR in the event of complications in recipient)
Damage during procurement	Lung, heart, liver, pancreas, kidney	Transplantable organ which is damaged during retrieval surgery. Organ lost to transplant	Surgical procedure error → Loss of suitable organ
Lung cancer found in donor *post mortem*	Multivisceral abdominal organ donation	Malignancy detected after procurement, organs already transplanted. No malignancy diagnosed in recipients after a 3-year follow-up	Risk of harm → donor disease without transmission (SAE)

C. Examples of serious adverse reactions (SARs) – recipients

Recipient SAR	*Organs*	*Case description*	*SAR type*
Metastatic breast cancer	Liver and kidneys	Donor with unknown breast carcinoma at the time of donation. Donor-derived metastatic malignancy diagnosed in 3 out of 4 recipients, 16 months to 5 years post-transplant	Harm to a recipient → malignancy transmission → carcinoma (Notify record n. 1959)
Removal of graft due to donor lymphoma	Kidney	Pre-transplant donor liver biopsy for evaluation of steatosis revealed extra-nodal non-Hodgkin lymphoma. One kidney had already been transplanted and was explanted immediately upon notification. Histology of the explanted graft did not reveal kidney involvement	Harm to a recipient → miscellaneous complications → loss of graft
Severe alloimmune thrombocytopaenia due to donor passenger lymphocytes	Liver, kidneys	Severe alloimmune thrombocytopenia caused by antibodies produced by passenger B cells present in the grafts (liver and kidney) from an HPA-1a mismatched donor. Transfusion with HPA-1a negative platelets, splenectomy and treatment with antithymocyte globulin were the therapeutic choices for each patient	Harm to a recipient → non-infectious, non-malignant transmissions → alloimmune reaction (Notify record n. 1656)
Tick-borne encephalitis virus (TBEV)	Liver, kidneys	Donor suffered head trauma following road traffic accident and had unsuspected TBEV infection. All three recipients (kidneys and liver) succumbed to meningoencephalitis caused by TBEV	Harm to a recipient → infection → viral (Notify record n. 1795)

Human T-lymphotropic virus type I (HTLV-I)	Liver, kidneys	Three recipients of solid organ transplants who developed subacute myelopathy within 2 years after becoming infected with HTLV-I from a single asymptomatic HTLV-I donor without risk factors (serology not performed pre-donation)	Harm to a recipient → infection → viral (Notify records n. 430, n. 431)
Strongyloides stercoralis	Heart, kidneys, kidney and pancreas	Unsuspected asymptomatic donors from endemic areas, retrospectively tested seropositive for *Strongyloides* antibodies. Recipients seroconverted and became symptomatic. Heart recipient developed hyperinfection syndrome and died	Harm to a recipient → infection → parasitic (Notify records n. 935, n. 936)

D. Examples of serious adverse reactions (SARs) – living donors

Living donor SAR	*Organs*	*Case description*	*SAR type*
Perioperative complications after living-donor nephrectomy	Kidneys	Retrospective analysis of 3 074 living kidney donors from 28 centres in the USA. The overall complication rate was 10.6 % and major complications defined by Clavien–Dindo grade ≥ 3 was 4.2 %. These included injury to bladder, bowel, diaphragm, spleen	Harm to a donor → miscellaneous complications → surgical site (Notify records nn. 807, 808, 809)
Perioperative complications after live lung (lobectomy) donation	Lung (lobectomy)	Retrospective cohort study to assess outcomes of live lung (lobectomy) donors in two US centres. Serious complications occurred in 18 % of donors; 2.2 % underwent re-operation and 6.5 % had early re-hospitalisation. Pneumothorax, pneumonia, pericarditis, pleural effusion, arrhythmia, empyema, haemorrhage, hydropneumothorax, atelectasis, bronchopleural fistula, haemoptysis were some of the complications described	Harm to a donor → miscellaneous complications → surgical site (Notify record n. 1096)
Perioperative complications after live (lobar hepatectomy) donation	Liver (right hepatic lobe)	Retrospective analysis of 392 donors, with complications classified as grade 1 (minor, 27 %), grade 2 (potentially life-threatening, 26 %), grade 3 (life-threatening, 2 %), and grade 4 (leading to death, 0.8 %). These included biliary leaks beyond post-operative day 7, bacterial infections, incisional hernia, pleural effusion requiring intervention, neuropraxia, re-exploration, wound infections and intra-abdominal abscess	harm to a donor → miscellaneous complications → surgical (Notify record n. 903)

16.3. Setting up an effective vigilance & surveillance system

European Directive 2010/53/EU on the Standards of Quality and Safety of Human Organs intended for Transplantation [1] sets the requirement for biovigilance programmes in European Union member states to report all SAREs to the appropriate HA. Systems and processes must be in place to fulfil this regulatory obligation, as well as meeting all the needs and objectives of biovigilance programmes, as described in this chapter. It is anticipated that organ procurement and transplant establishments in other parts of the world will follow similar local regulatory requirements.

There are essential aspects to consider when planning how to design and implement an effective V&S system, including the following:

- who are the individuals that will be expected to notify any adverse occurrence;
- when, how and to whom the occurrence should be notified;
- how incidents will be managed, classified and reported to the HA as required.

In this section, we describe general organisation aspects that need to be taken into consideration when planning a V&S system.

16.3.1. Overall structure

Robust structure and appropriate resources are critical to the efficiency of biovigilance programmes. There may also be an extended risk of harm to other organ or tissue recipients, and to the wider community, in the case of transmissible diseases; SAREs may involve diseases that are not initially apparent and only become evident after donation and transplantation. Not all of these incidents will meet the threshold of an SAR or SAE – but for a system to be as effective as possible, it is essential that incidents that do not initially classify as SAREs are nevertheless communicated so that they can be collated and any recurrent themes or issues can be identified and acted upon. The team receiving notification of adverse occur-

rences will ultimately comply with the notification requirement to the HA.

Preferably, one specific body or authority should be appointed to run the biovigilance programme within a given jurisdiction [1]; this jurisdiction may be at national or regional level and this will be defined by factors specific to the member state. This authority should be the link to all parties involved and should be responsible for establishing, maintaining and regulating the system by co-ordinating all steps in the process.

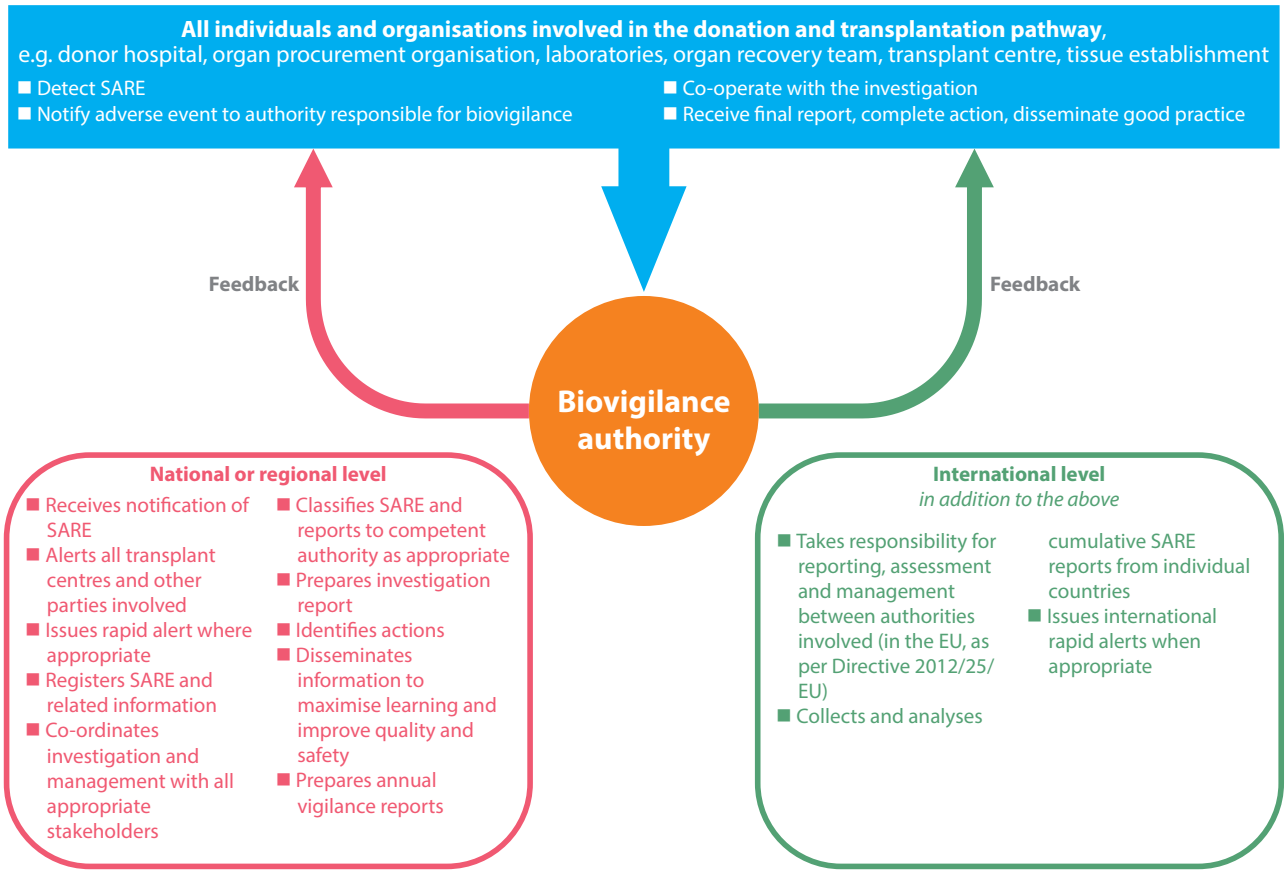
Member states should adopt a V&S reporting system that is appropriate for the style and structure of their organ donation and transplantation infrastructure. In considering what is the most appropriate system, there should be assessment of the benefits, capacity and sustainability of having a single national system *versus* regional systems linked to a central office for reporting of incidents. In the latter case, relationships and roles need to be clearly defined to ensure a seamless process.

Co-ordination and communication between various systems of vigilance (e.g. tissue and cell vigilance, medical devices vigilance, pharmacovigilance) should also be in place, both at the local level (centres) and at the HA level.

16.3.2. Human resources, education and training

The agency responsible for biovigilance must be appropriately resourced to deliver its function effectively. Staff in biovigilance programmes must be appropriately trained and familiar with the core concepts of V&S in transplantation, have a good understanding of the entire organ procurement, donation and transplantation pathway in their country or region, and be knowledgeable of all standard operating procedures and process descriptions. They must also be competent to co-ordinate causation analysis exercises, severity grading and classification of incidents into SAR or SAE. In their role as co-ordinators, they should be competent to network with all parties concerned and seek appropriate expert advice as required.

Figure 16.1. **Illustrative flow for the detection and reporting of adverse events and reactions**



SARE: Serious adverse reaction and event

All stakeholders, Health Authorities (HA), organ procurement organisations (OPOs) and healthcare professionals in donor hospitals and transplant centres should promote and adhere to a culture that encourages reporting, maintaining a transparent and non-punitive environment for the benefit of patients and donors.

Education should focus on the understanding and the real-life application of biovigilance principles. Stakeholders should be informed how to use notification systems, how to report and how to benefit from the outputs of a vigilance system. Biovigilance programmes must be committed to sharing learning from incidents; this involves production of incident reports, case studies and regular bulletins, always observing confidentiality and avoiding publication of identifiable information.

16.3.3. Quality management system

A robust quality management infrastructure is key for the reporting and investigation of SAREs at local, regional, national or international level. Some aspects will be mentioned here but Chapter 17 covers the subject in detail.

16.3.4. Technical resources (including incident notification system)

Electronic quality management software systems are essential tools for the efficient running of a biovigilance programme. Electronic reporting of incidents is vital for consistency, accuracy and speed of communication, as well as facilitating audit trail and data analysis. Ideally, there should be a national, centralised, web-based biovigilance network, integrated with other registries related to organ procurement and transplantation (e.g. transplant registry with deceased donor, waiting list and transplant recipients data). Lack of accessibility to such facilities should not preclude establishment of V&S programmes but it should be part of the development and expansion plans; these information technology tools should be implemented whenever possible because they are associated with overall increased efficiency, quality and safety.

16.3.5. Archive of donor and recipient serum and plasma

Although prolonged donor serum or plasma storage is not a regulatory requirement set by the EU directive, it features in a number of national guidelines and is widely accepted as essential practice. It is highly desirable that HA should request archiving of such material for the specific purpose of vigilance investigations (see Chapter 6). Recipients' pre-transplant blood should also be archived; availability of donor and recipient(s) blood samples may help inform investigations of incidents and assessment of imputability [2, 4] in case of suspected donor-derived disease transmission (see Chapter 9 for analysis of donor-derived malignancy transmission). Laboratories have to consider the preferred analyte for storage, taking into account the need to perform serological and molecular assays.

16.3.6. Storage and traceability of incident investigation data

All SARE cases together with accompanying datasets and reports must be properly documented, archived and kept in a way that allows easy accessibility and review. This documentation forms part of the quality management and quality control documentation of organ procurement organisations, transplant centres and HAs or their delegated bodies. The archived documentation must also be in line with national provisions on the protection of personal and medical data.

16.3.7. Audit of processes and transplant outcomes

The authority responsible for biovigilance of MPHOs should issue appropriate guidance for the collection of relevant post-transplant information to evaluate the quality and safety of transplanted organs. Outcome data, incident patterns and trends and other auditable parameters should be monitored under the broad quality and safety framework. These data should relate to living donors and organ recipients.

16.3.8. International V&S co-operation and communication

Rapid communication, data exchange and co-operation across countries is vital in any V&S system, particularly so when organs are imported from and exported to other countries. Appropriate infrastructure and processes must be in place to enable this.

16.4. Practical steps in biovigilance

Adverse occurrences may present in various forms at different time points and they may arise as a

result of a combination of factors. These unexpected events may be identified or become apparent quite late (months to years) after the implantation of a graft, hence the link to the donation and transplantation pathway may not be easy to make. In the case of disease transmission, for example, lack of understanding of the pathogenesis and the epidemiology of the condition may hinder the ability to recognise a potential donor-derived disease; whenever there is doubt, it is always prudent to consult with appropriate specialists.

This section describes a simplified, step-by-step process of notifying, investigating and taking all the necessary actions following the identification of an untoward occurrence.

16.4.1. Detection of cases

There is a collective responsibility to maintain awareness of and promote good practice in all aspects of donor and recipient safety. All professionals involved in the donation and transplantation processes, including those involved in post-transplant care, must remain attentive to unusual occurrences, unexpected results or outcomes, errors and 'near misses'. As soon as they are identified, such occurrences must be notified according to local or national protocols.

16.4.2. Incident notification to the Biovigilance office

Standardised reporting forms should be provided by the authority responsible for biovigilance; a minimum data set must exist for initial reporting of events and this must be defined locally, so as to fit in with individual systems and processes; some examples are illustrated in appendices 25-27. All notifications should provide a documented account of the incident and be in accordance with local quality management systems; online submission through a secure portal or other forms of electronic submission are the preferred options and should be used whenever possible. Local protocols must be followed and, where initial verbal contact is made to ensure rapid action, this must always be followed by written notification.

In cases of international organ exchange, the notification form, all other data and any test results should be provided in the English language.

16.4.3. Communication of incident and Rapid Alert system

16.4.3.1. *Sharing initial incident notification*

The organisation responsible for biovigilance is responsible, upon receipt of an incident notification, for assessment and timely onward communication of information to relevant transplant centres and other establishments, as appropriate. Protocols must exist that describe such processes in a clear and objective way; they must contain criteria for the communication of incidents, with instructions on the mechanism, speed and extent of dissemination. This process must contain a 24/7 pathway to ensure proper handling of urgent medical information. Figure 16.2 illustrates a communication cascade triggered by an SAR notification to the Biovigilance office.

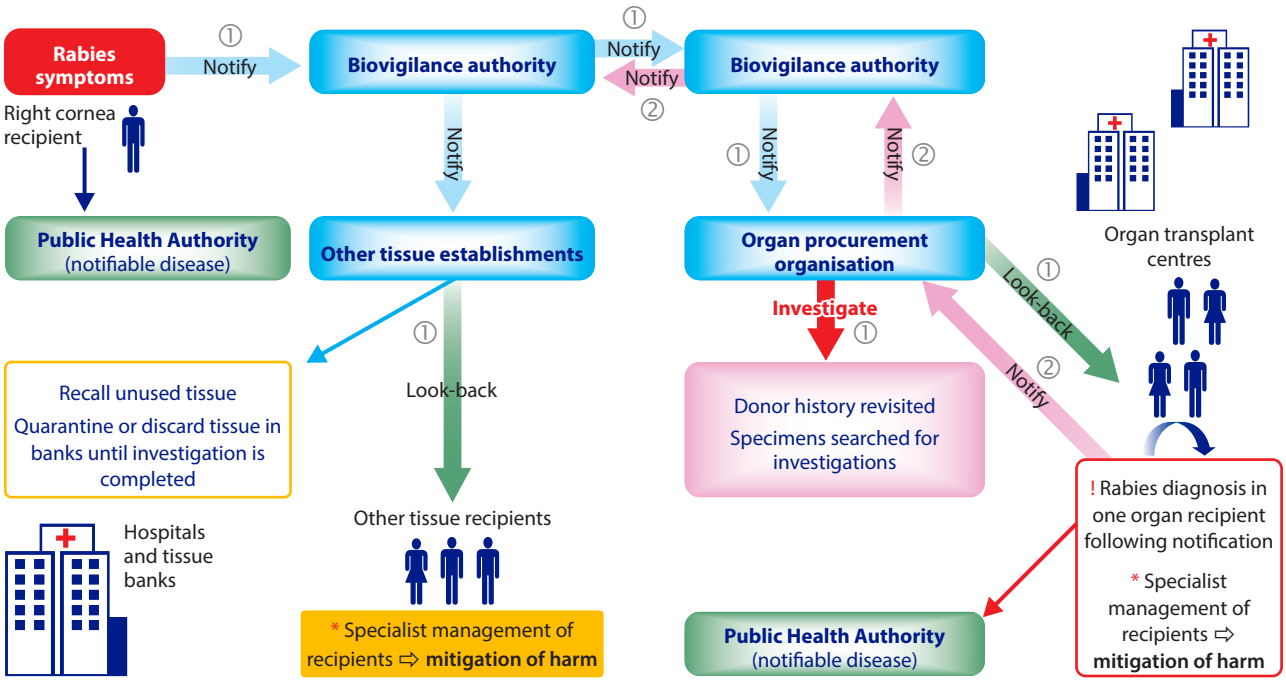
16.4.3.2. *Rapid Alert*

Rapid Alert is a real time communication sent out by the Biovigilance office to appropriate stakeholders whenever there is a possibility that immediate action is required for harm mitigation to organ and tissue recipients (e.g., notification of fulminant liver failure in a lung recipient following development of primary *Herpes simplex* virus infection in the early post-transplant period). The Biovigilance office acts immediately by sending a rapid alert and phoning all centres where organs from the common donor have been transplanted. Early assessment and commencement of anti-viral therapy are essential determinants of improved outcomes in a condition with otherwise high mortality rate.

The European Commission runs a secure platform to connect member states in the case of an SARE with potential cross-border impact. This platform is also useful for alerting relevant organisations to transmissible disease outbreaks and problems with diagnostic devices or assays. The objective of the platform is to ensure rapid dissemination of urgent information and implementation of immediate measures to ensure patients' safety.

In some specific circumstances, a particular SARE may require rapid communication nationally or internationally to facilitate urgent actions where there is risk of broader public health impact, such as a recall of products or critical materials (e.g. microbiologically contaminated organ preservation fluid where a fault in manufacturing is being investigated). The SoHO V&S project [4] has enumerated some examples of such situations.

Figure 16.2. **Illustrative case of an unexpected, serious infection reported in a transplant recipient and subsequent necessary actions**



Multi-directional flow of actions required in complex cases, requiring prompt action, extensive networking and specialist input. The example given is of a rare infectious disease, but more common conditions can also present with the same level of complexity.

16.4.4. Incident investigation

This is a fundamental step in the biovigilance process. Following communication of an incident, the receiving V&S body is responsible for the timely gathering of crucial information, mapping of events, processing and analysis of facts, with final production of a meaningful incident report. Findings, recommendations and actions must be clearly laid out. This process requires trained staff with the correct skillset to deliver all the functions that will be described in this section. In their co-ordinating role, staff must seek advice of experts, depending on the nature of the occurrence and must also have the ability to link relevant parties, so as to ensure efficient collaborative work.

16.4.4.1. *Root cause analysis*

Investigation of incidents that have caused, or had the potential to cause, harm to donors and/or recipients requires a structured approach to identify the factors that resulted in the event.

The aim of this process of root cause analysis (RCA) is to understand the circumstances of the incident, identify cause(s) and contributors, address deficiencies and learn how to prevent similar incidents from happening again. This should be delivered by a designated team and a co-ordinator, who should be trained to fulfil clinical governance and quality requirements to conduct investigations objectively and efficiently.

The following essential steps need to be considered:

a. Collection of information – to include full details of what happened, as well as relevant policies and procedures. It is strongly advised that data be collected in a systematic way, using electronic forms or set templates.

Generally, and especially so with disease-transmission events, it is very important to organise detailed and systematic information gathering to enable proper assessment; an indicative list is shown below. The format used in the Notify Library [5] reports can also be reproduced or used for guidance:

i. When, how and why was the occurrence detected.
ii. Epidemiology, signs, symptoms, interventions and outcome in the index case.
iii. Pre-transplant evidence of disease or infection in donor or in the recipient.
iv. Outcome in other recipients.
v. Availability of donor and recipient samples, microbial organism strains for appropriate analysis.

b. Mapping of information – timelines, flowcharts, chain of events; this can make it easier to identify gaps in information, to reveal contributing factors and highlight deficiencies in processes.

c. Identification of significant contributing factors – depending on the incident, it may also be useful to conduct a face-to-face meeting with personnel who were involved in the activities within which the incident took place, especially if the occurrence is thought to have resulted from a breakdown in process or communication. This can be useful to develop an idea of the environment in which the event took place to establish parameters that may have the most significant impact on reducing likelihood of recurrence

d. Causal analysis, recommendations and actions – agreement on causation and understanding of interacting factors must lead to formulation of actions and recommendations. This should be followed by implementation of solutions.

e. Final Incident Investigation Report – a fundamental part of the whole process; it must contain a synopsis of the investigation, key facts and findings, conclusions and recommendations in a clearly understandable language and format. This format and structure may vary depending on the local requirements stipulated by designated authorities; simplified versions of the main report may be used for different purposes. Importantly, this should be a consensus document supported by all parties and stakeholders involved. Confidentiality of patients, professionals and establishments needs to be observed, as appropriate.

16.4.5. Assessment and grading of adverse events and reactions

The European Union Standards and Training for the Inspection of Tissue Establishments Project (Eustite) describes a tool for the assessment of severity and impact in case of recurrence. It was originally developed for tissues and cells but some V&S programmes for organ transplantation make use of the impact matrix to objectively document the proportionality of the response to individual SAREs. Its use is by no means a legal requirement in the field of organ donation and transplantation and in fact many established V&S programmes choose not to use it.

The aim is to facilitate incident management, analysis and determination of magnitude and nature of response required. By having outputs of the vigilance system expressed in a standardised format, trend analysis and comparisons across different registries and V&S programmes are made possible.

There are five steps in this process, which are discussed below; they are partly based on the US Disease Transmission Advisory Committee (DTAC) decision tree [6], a comprehensive tool for assessing imputability (step 2), and partly on the Eustite impact-assessment tool. The five steps are:

1. Analysis of severity of incident
2. Assessment of imputability in an SAR or causes in an SAE
3. Estimation of likelihood of recurrence
4. Evaluation of consequences and impact of recurrence at the individual, system and organ-supply level
5. Decision on magnitude and nature of response.

16.4.5.1. *Severity grade*

The severity scale from the Eustite and SoHO V&S, which was originally developed for tissues, can be used for grading organ-related notifications (see Table 16.2). In Europe, there is a statutory requirement to notify organ V&S programmes of all severe occurrences (serious, life-threatening or leading to death). Non-serious occurrences may be dealt with as quality incident events, according to local protocols.

Table 16.2. **Severity scale for adverse events and reactions**

Severity	Comments
Nil	no harm, no risk (patient not informed as there was no risk of harm)
Non-serious	mild clinical/psychological consequences (with no need for hospitalisation and no anticipated long-term consequence/disability)
Serious*	• hospitalisation or prolongation of hospitalisation, and/or • persistent or significant disability or incapacity, or • medical or surgical intervention to preclude permanent damage, or • transmission of a severe disease or prolongation of a disease
Life-threatening*	• the need by a living donor or transplant recipient for a major intervention (vasoactive drugs, intubation/mechanical ventilation, admission to intensive care) to prevent death, or • transmission of a life-threatening disease
Death*	death

*Mandatory reporting to the Health Authorities as SARE according to national regulation in the European Union.

Source: adapted from Eustite and SoHO V&S [4, 7].

16.4.5.2. *Imputability or causes*

All SARs should be graded in terms of imputability; the grading provided by the EUSTITE and SoHO V&S projects can be used as guidance [4, 7]. Table 16.3 shows an adapted version of both grading systems and also includes the US DTAC classification criteria [8]. There are also other methods of assessing imputability [6], with overlapping approaches on how to draw final conclusions.

Common to all approaches is that the evaluation of imputability must be based on precise, evidence-based, clinical, epidemiological and scientific facts. The ongoing Notify project [9] provides examples of adverse reactions and addresses imputability grading in a systematic way. When considering whether or not a donor-derived disease has been transmitted to solid-organ graft recipients, it is very important to consider local epidemiology and natural history of the disease in question, as well as knowledge of its pathogenesis. In infectious disease transmission, characteristics of the organism involved are essential when determining common source and transmission linkage; the same applies to malignancies. With advancing technologies, pathogen strain comparisons can nowadays be done in much greater detail, reinforcing the fact that finding the same agent in both donor and recipient may not be sufficient to assign donor imputability, unless in certain specific circumstances.

Table 16.3. **Imputability grading in SARs**

Grading	Adapted from EUSTITE and SoHO V&S [4, 5, 7]	Criteria for infectious and malignant transmissions, adapted from the US Disease Transmission Advisory Committee [6]
Not assessable	Insufficient data for imputability assessment	Insufficient data for imputability assessment
Intervention without disease transmission		• Intervention given to recipient(s) with intention to prevent disease transmission, and • No disease transmission in those who received the intervention
0: Excluded	Conclusive evidence beyond reasonable doubt for attributing an adverse reaction to alternative causes There is evidence clearly in favour of attributing the adverse reaction to causes other than the process or transplanted organ	Suspected transmission and fulfilment of at least one of the following conditions: • Clear evidence of an alternative cause • The appropriate diagnostic tests performed have failed to document infection by the same pathogen in any transplant recipient from the same donor • Laboratory evidence that the recipient was infected with the same pathogen or had a tumour before transplant
1: Possible	The evidence is not clear for attributing the adverse reaction to the process or transplanted organ, or to alternative causes	Suspected transmission and either: • Laboratory evidence of the pathogen or tumour in a single recipient or • Data suggest transmission but are insufficient to confirm it
2: Probable/ likely	The evidence is clearly in favour of attributing the adverse reaction to the process or transplanted organ	The following two conditions are met: • Suspected transmission and • Laboratory evidence of the pathogen or the tumour in a recipient And it meets at least one of the following conditions: • Laboratory evidence of the same pathogen or tumour in other recipients • Laboratory evidence of the same pathogen or tumour in the donor If there is pre-transplant laboratory evidence, such evidence must indicate that the same recipient was negative for the pathogen involved before transplant.
3: Definite / certain/ proven	The evidence is conclusive beyond reasonable doubt for attributing the adverse reaction to the process or transplanted organ	All the following conditions are met: • Suspected transmission; • Laboratory evidence of the pathogen or the tumour in a recipient; • Laboratory evidence of the same pathogen or tumour in other recipients (if multiple recipients); • Laboratory evidence of the same pathogen or tumour in the donor. If there is pre-transplant laboratory evidence, such evidence should indicate that the same recipient was negative for the pathogen before transplant.

16.4.5.3. *Likelihood of incident recurrence*

For every SAR or SAE, the likelihood of recurrence should be considered and can be graded according to a scheme like that of the EUSTITE and SoHO V&S projects; see Table 16.4 [4, 7].

Table 16.4. **Assessing the likelihood of recurrence of an adverse reaction or event**

1	Rare	Difficult to believe it could happen again
2	Unlikely	Not expected to occur again
3	Possible	May occur occasionally
4	Likely	Expected to occur again, but not persistently
5	Probable	Expected to occur again on many occasions

Note: The score for likelihood of recurrence should be entered in the impact matrix, Table 16.6.

16.4.5.4. *Impact and consequences of incident recurrence*

The impact and consequences of SAREs can be assessed, as shown in Table 16.5, which is meant to assist practitioners and regulators in planning their response to a given adverse reaction or event, taking into account broad consequences, beyond the individual patient affected or potentially affected. The impact can be scored at three different levels: individual, system and organ supply level.

The likelihood of recurrence and the impact of recurrence are considered as interacting factors that can inform the nature and magnitude of a response that is proportionate to its degree of severity, the likelihood of recurrence and the consequences incurred in the event of recurrence. The future impact may be reduced, either by reducing the likelihood of recurrence through preventive measures (horizontal axis) or by reducing the impact of any recurrence (vertical axis); the latter could be achieved by improving the treatment options available, for example.

16.4.5.5. *Level of response*

The two-dimensional impact matrix developed by the EUSTITE and SoHO V&S projects has been designed to help organisations responsible for biovigilance decide on the level of response that might be appropriate; this may include urgency and scale of implementation of corrective, therapeutic or preventive measures (see Table 16.6).

As previously mentioned, the use of this impact matrix for assessment of incidents in organ transplantation varies across different services. It is not mandated, and it serves as a complementary tool to help inform the nature of the response required following an incident. It supplements – and is not a substitute for – a full incident investigation (described in §16.4.4).

Table 16.5. **Assessing impact of an SARE in case of recurrence**

Impact level		**On the individual(s)**	**On the system**	**On the organ supply**
0	Insignificant	Nil	No effect	Insignificant
1	Minor	Non-serious	Minor damage	Some transplantations postponed
2	Moderate	Serious	Damage for a short period	Many transplantations cancelled or postponed
3	Major	Life-threatening	Major damage to the system – significant delay to repair	Significant cancellations of transplantations
4	Catastrophic/extreme (or Severe)	Death	System destroyed – need to rebuild	All transplantations cancelled

Note: The score for impact level should be entered in the impact matrix of Table 16.6.
Source: adapted from EUSTITE and SoHO V&S [4, 7].

Table 16.6. **Impact matrix**

Impact of recurrence	**Likelihood of recurrence**				
	1 Rare	**2 Unlikely**	**3 Possible**	**4 Likely**	**5 Certain/ almost certain**
0 Insignificant	0	0	0	0	0
1 Minor	1	2	3	4	5
2 Moderate	2	4	6	8	10
3 Major	3	6	9	12	15
4 Catastrophic/extreme	4	8	12	16	20

Source: EUSTITE and SoHO V&S projects [4, 7].

Score 0 to 3: The HA will keep a watching brief and leave the involved parties to implement corrective and preventive measures.

Score 4 to 9: A more proactive response is required; an inspection that focuses on the SARE may be necessary, with the corrective and preventive actions to be followed up. Written communication to professionals working in the field might be appropriate.

Score 10 to 20: A very active response is required. An incident group or task force may need to be set up in order to develop and agree on an action plan. Broader involvement of other authorities or policy makers may also be necessary.

16.4.6. Incident investigation report

This has also been addressed in 16.4.4, under the section on full incident investigation.

The production of a final report is a requirement set by the HA, but all stakeholders involved in the incident investigation must also receive concluding feedback from the responsible biovigilance team. This is a critical way to acknowledge the importance of incident reporting and thus maintain a good level of engagement from everybody involved in organ donation and transplantation. This information should be disseminated in order to prevent recurrence and be used as a learning experience.

The format of the report usually follows the sequence of steps taken during the incident investigation. Identifiable information (e.g. patients, donors, transplant centres, donor hospitals, professionals involved) must be redacted according to distribution lists.

Legal oversight may be required, depending on the nature of the incident. Communications teams may need to be involved in certain cases, where media and public interest may be high. The investigating team should follow existing protocols to address these issues.

16.5. Communication with donor families, living donors and recipients

Effective and timely communication in the setting of a non-blame culture is fundamental in biovigilance and should be promoted and practised at all times [10]. The mechanisms for maintaining effective communication have been covered in earlier parts of this chapter.

Chapter 19 of this guide is dedicated to the very important theme of communication with recipients, donor families and living donors. Any communication should be in accordance with established protocols; in the UK, for example, the professional obligation of the duty of candour places a statutory and ethical responsibility on organisations to be open and honest with patients, their families and service users when something goes wrong that appears to have caused (or could in the future lead to) significant harm. All communication should be conducted sensitively and clearly, by a member of the team who has full understanding of the incident. Explanation of the occurrence and its significance for the individual's health and information about the condition (in case of infection or malignancy transmission, for example) or possible interventions such as testing and treatment should be provided both orally and in writing. Prompt access to other professionals and specialist referral should be arranged as appropriate.

There should be a proportionate level of involvement from the press office and legal teams of the involved organisations so that all necessary external communications are handled professionally and appropriately.

16.6. Conclusions

As with any health intervention, solid-organ transplantation is associated with risk, and this risk must always be balanced against the anticipated life-saving or life-preserving benefit of the transplant itself. We hope this chapter has demonstrated that having a robust and effective V&S system provides a mechanism to identify any likely risks and a structured way of managing when things go wrong, in order to minimise further harm. Biovigilance provides a powerful safeguarding tool for donors, patients, health professionals and HAs to promote good practice and continuous improvement of care. The goal of any biovigilance system is to optimise the overall benefit for recipients by mitigating risks and correcting deficiencies, thus promoting access to safe organs and high-quality transplantation.

Research agenda

From the literature and discussion of the available evidence, several topics have been identified for which evidence is inconsistent, insufficient or non-existent. The authors of this chapter recommend that future research in the field of biovigilance should include or take into account the following knowledge gaps:

1 Behavioural science research to understand attitudes towards vigilance systems, fear of reprehension, barriers to sharing of mistakes and

other factors influencing detection and reporting of incidents.
2 Development of extended framework to support professionals involved in vigilance programmes, under the principle of the duty of candour, and all other individuals affected by the events, including donors, patients and their families.
3 Development of efficient tools or modules to be built into quality system programmes, to enable efficient running of organ vigilance programmes.
4 Educational programmes and platforms for the dissemination of knowledge, including the methodology for investigation of incidents and sharing of lessons learnt.
5 Development of consensus guidance on investigation and establishment of imputability in biovigilance, with special focus on transmission of malignancies and infections.
6 In regard to preparedness for future high-impact threats, there is a need for formal and co-ordinated international collaboration that facilitates the sharing of data on possible threats to MPHO safety and availability, particularly in relation to new pathogens, outbreaks and pandemics.
7 Where the theoretical risk of transmission of disease through the transplanted graft exists, research into the mechanisms and determinants of transmission is required, as is the case for SARS-CoV2, for example.

16.7. References

1. Directive 2010/45/EU [*recte* 2010/53/EU] of the European Parliament and of the Council of 7 July 2010 on standards of quality and safety of human organs intended for transplantation, available at https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32010L0053&from=EN, accessed 21 July 2021.
2. Report on the use of the European Registry of Registries. Efretos project, available at https://webgate.ec.europa.eu/chafea_pdb/assets/files/pdb/20081101/20081101_do9-00_oth_en_ps.pdf, accessed 21 July 2021.
3. VISTART WP4. 'Guidelines on horizon scanning for identifying new risks related with the donation of substances of human origin', available at www.notifylibrary.org/sites/default/files/VISTART_WP4_D4.3_Guidelines%20on%20Horizon%20scanning.pdf, accessed 21 July 2021.
4. SoHO V&S Guidance for Competent Authorities: Communication and investigation of serious adverse events and reactions associated with human tissues and cells, available at www.notifylibrary.org/sites/default/files/SOHO%20V%26S%20Communication%20and%20Investigation%20Guidance.pdf, accessed 21 July 2021.
5. The Notify Booklet: Vigilance and Surveillance (V&S) of medical products of human origin (MPHO), available at www.notifylibrary.org/sites/default/files/Booklet_2018_1.pdf, accessed 21 July 2021.
6. Green M, Covington S, Taranto S *et al.* Donor-derived transmission events in 2013: a report of the Organ Procurement Transplant Network Ad Hoc Disease Transmission Advisory Committee. *Transplantation* 2015 Feb;99(2):282-7. DOI: https://doi.org/10.1097/TP.0000000000000584; available with expanded graphics at http://download.lww.com/wolterskluwer_vitalstream_com/PermaLink/TP/B/TP_2015_01_13_GREEN_TPA-2014-1383_SDC1.pdf, accessed 21 July 2021.
7. Fehily D, Sullivan S, Noel L *et al.* Improving vigilance and surveillance for tissues and cells in the European Union: Eustite, Soho V&S and Project Notify. *Organs Tiss Cells* 2012;15:85-95.
8. Garzoni C, Ison M. Uniform definitions for donor-derived infectious disease transmissions in solid organ transplantation. *Transplantation* 2011;92:1297-1300.
9. Fehily D, Strong DM, Minutoli D *et al.* Sharing vigilance experience and knowledge globally: a preliminary overview of the Notify Library. *Organs Tiss Cells* 2013;16:117-25.
10. Avsec D, Breidenbach T, Lingemann M, Logar Zakrajšek B. *Communicating about organ donation and transplantation: a handbook on theoretical and practical aspects*. DeutcheStiftung Organisation, Slovenija-transplant, 2016. Project Foedus, available at www.dso.de/SiteCollectionDocuments/Communicating_about_organ_donation_and_transplantation.pdf, accessed 21 July 2021.

Related material

Appendix 25. Biovigilance standardised notification form for adverse events and reactions (France, English-language version)
Appendix 26. Incident notification form, Germany (English-language version)
Appendix 27. Incident notification form, United Kingdom

Chapter 17. Achieving and measuring quality in organ donation and transplantation

17.1. Introduction

This chapter outlines the general principles of quality management systems in organ donation and transplantation. It is addressed to Health Authorities (HAs), managers and health professionals directly involved in the process, with a special emphasis on donation and transplantation co-ordinators because they are central actors, involved in many steps in the chain from donation to transplantation. Moreover, because donation/procurement and transplant activities involve different aspects, different organisations and different health professionals, quality management is examined separately for these two types of activities.

After introductory remarks on quality management in general, and quality management applied to organ donation and transplantation in particular, this chapter provides separate reviews of government and HA responsibilities, quality management in organ donation and finally quality management in organ transplantation.

17.2. General introduction to quality management

The quality of healthcare has always been a major concern for healthcare professionals who, in one way or another, even without using any specific or recognised methodology, have striven to achieve excellence in their work. That commitment is part of the job.

The development of instruments that enable quality to be measured has been essential in turning this concern into a way of working. Once it became possible to measure – or evaluate – quality, the focus shifted from quality control to quality assurance and, since the 1990s, towards continuous quality improvement.

As well as a commitment to excellence, continuous quality improvement requires a method. The aim is to continuously improve a process in an organisation for the purpose of fulfilling or even exceeding the (internal and/or external) expectations and requirements of the customer/patient. This can be achieved through quality management systems, these being any systems that help an organisation to establish the methodology, responsibilities, resources and activities needed to obtain good and measurable results.

Well-established models for quality management used in the healthcare sector include ISO (International Organization for Standardization), JCAHO (Joint Commission on Accreditation of Healthcare Organizations), EFQM (European Foundation for Quality Management) and KTQ (Cooperation for Transparency and Quality in Healthcare) [1-4]. A comparison of these models reveals the following:

a. There are few philosophical differences. All have the 'customer' (or patient) as the focus of the organisation and of the quality.

b. In terms of practical application, all four models involve a monitoring scheme. The actual situa-

tion is compared with pre-established standards (ISO and JCAHO) or criteria (EFQM and KTQ) to identify where improvements need to be made within the aspects assessed in the respective models; problems then have to undergo cycles of improvement if the models are actually to be of use in the dynamics of quality improvement.

c. Although the JCAHO and KTQ models are the ones specific to healthcare services, the other two, which are either of generic or industrial origin, have tried to produce specific adaptations for healthcare services. In fact, since 2012 ISO has had a new standard specifically on quality management systems in healthcare services (EN ISO 15224:2012).

All these four models can be facilitators of commitment to quality and may be used in the healthcare sector. However, their wider diffusion at international level and their specific design directed at healthcare services make ISO and JCAHO the two most-used models. Regardless of the fact that some important aspects of donation and transplantation are accredited in many hospitals (e.g. certification of immunological, haematological or biochemistry laboratories, pathology), in some European countries several donation and transplantation programmes have already been accredited in a global way (e.g. Spain: ISO 9001 accreditation).

17.3. Applied quality management in organ donation and transplantation

As in other healthcare activities, careful attention must be paid to all quality aspects of the entire process, i.e. from donation to transplantation and follow-up, in order to ensure their safety and efficacy and to maintain public and professional confidence. Several different quality management systems (as we have previously reviewed) can be applied to different aspects/parts of the transplant chain, from donor identification to allocation and transplantation or disposal of organs, including appropriate follow-up.

To establish and maintain a quality management system is the responsibility of the healthcare professionals involved in donation and transplantation processes, but also of governments and HAs in charge of healthcare systems in general and of the transplant system in particular.

In the EU, this common responsibility of HAs and health professionals was confirmed with the adoption in July 2010 of Directive 2010/53/EU on standards of quality and safety of human organs intended for transplantation [5]. Indeed, the EU member states "shall ensure that a framework for quality and safety is established to cover all stages of the chain from donation to transplantation or disposal" (Article 4). To do so, Article 17 provides that "Member States shall designate one or more competent authorities" to establish the framework for quality and safety, ensure that procurement organisations and transplantation centres are authorised and controlled or audited regularly, and take other measures described below. Regarding health professionals, Article 12 provides that "Member States shall ensure that healthcare personnel directly involved in the chain from donation to transplantation or disposal of organs are suitably qualified or trained and competent to perform their tasks and are provided with the relevant training".

The EU Action Plan on Organ Donation and Transplantation (2009-2015), which aimed to strengthen co-operation between member states [6], also explicitly provided for common action on quality improvement programmes (QIPs), with its Priority Action 2: "promote quality improvement programmes in every hospital where there is a potential for organ donation", while the other nine priority actions also refer to the "exchange of best practices", "twinning projects and peer reviews" and the development of common tools, thus fully in line with a logic of continuous quality improvement.

The quality management system in place at a procurement organisation or transplant centre must be fully documented and must ensure that all critical processes are specified in appropriate instructions and are carried out in accordance with relevant standards and specifications. Management should review the system at regular intervals to verify its effectiveness and introduce corrective measures if deemed necessary.

Applying a systematic approach to quality management in this context involves separate reviews of the following:

a. government and HA responsibilities;
b. quality management in organ donation;
c. quality management in organ transplantation.

17.4. Government and Health Authority responsibilities in organ donation and transplantation: a framework for quality and safety

If they are to reduce the risks and maximise the benefits of transplantation, Council of Europe member states need to ensure that a framework for quality and safety is established to cover all stages of the chain from donation to transplantation or disposal. That framework should act to integrate the activities carried out in all procurement and transplant centres, and in establishments responsible for allocation/distribution, in order to ensure the highest possible quality, safety and transparency of the process while increasing the number of organs available.

The recovery and distribution of organs has to be properly regulated. The HAs of the state must play their key role in establishing a legal and organisational framework to ensure the quality and safety of organs during the donation and transplantation process, and in evaluating their quality and safety throughout post-operative patient recovery and the subsequent follow-up. According to Directive 2010/53/EU [5] and other major recommendations [6-13] in the field of organ donation and transplantation, the quality and safety framework should include:

a. A system for authorisation and audit/inspection of organ procurement and transplant organisations, by which quality and safety are ensured for both recipients and living donors. Such organisations should have in place proper systems, suitably qualified or trained and competent personnel and adequate facilities and material [7].

b. Designation of a non-profit national or international body responsible for the allocation and distribution of organs. As emphasised by the Committee of Ministers of the Council of Europe in its recommendations to member states on the background, functions and responsibilities of a national transplant organisation, it is preferable to have a single, officially recognised, non-profit-making body with overall responsibility for donation, allocation, transport, traceability and accountability [9].

c. An organ-allocation system with strong guarantees, in terms of both equity and efficiency, to ensure optimal transplant use, especially considering the technical constraints inherent in organ recovery, transportation and quality maintenance. This system should support transparency, traceability and external audit of decision making. The rules for allocation should be clearly defined for each organ and made available to health professionals, patients and the public. The guidelines governing the allocation criteria and the distribution of organs should be developed and implemented by common agreement with a group of experts involved in organ transplantation. These rules must be regularly re-evaluated, taking technical advances into account [8].

d. A requirement to establish a comprehensive framework for quality and safety for the whole chain, with the adoption and implementation of standard operating procedures (SOPs) combined with standard documentation (protocols) for [5]:

i. verification of donor identity;
ii. verification of the details of the consent authorisation (or absence of any objection) of the donor or their family, in accordance with the national rules that apply where donation and procurement take place;
iii. verification of the completion of the organ and donor characterisation;
iv. procurement, preservation, packaging and labelling of organs;
v. transport of organs;
vi. assurance of traceability;
vii. accurate, rapid and verifiable reporting and management of serious adverse events and reactions.
viii. a system that allows traceability of each donated organ (and tissue) from the donor and the donation process to each recipient and vice versa. This system must allow donor material to be traced to either its source or its destination. Each donor/component (the terminology used in resolutions of the European Commission, which refers to the organs, parts of organs and any biological material of the donors) should be assigned a unique identifier, used to link the donor to all tests, records, transplants and other material and, for tracking purposes, to the recipient.

e. A vigilance system to provide mechanisms for the safety of donors and recipients, managed by national and/or supranational institutions. This system should ensure rapid reporting and investigation of any undesirable event occurring in relation to donation and transplant services (e.g., unexpected or unintentional

transmission of an infectious or malignant disease from donor to recipient), so that corrective and/or preventive actions can be taken immediately. Any kind of serious adverse reaction in an organ recipient that is suspected to be of donor origin, or related to the donation process, needs to be reported without delay to all other institutions receiving organs or tissues from the same donor. The scope of such a system should cover all the steps of the process, from donation to transplantation, as well as the follow-up period, including a procedure for data collection according to legal requirements. The system must also inform all tissue banks in cases where tissues and/or cells have been procured from the same donor [5].

f. If necessary, a system to exchange organs with other countries and/or with international or European organ-exchange organisations, regulated and supervised by the HAs, to increase the probability of providing organs for patients in special situations with lower chances of finding compatible organs within their own country (e.g., small children in need of liver, intestinal or heart transplantation, patients in life-threatening situations or conditions in need of urgent organ transplantation, difficult-to-match recipients highly sensitised against human leukocyte antigens). Organ exchange with other countries or organ allocation organisations should be allowed only where equivalent standards of quality and safety are met [10].

g. A system to ensure that strict confidentiality rules and security measures are in place for the protection of donors' and recipients' personal data at all stages of the donation and transplant process, including traceability and vigilance systems. The HA may also consult the national data-protection supervisory authority in relation to developing a framework for the transfer of data on organs to and from other countries [5].

h. A system to ensure that the healthcare personnel directly involved, at all stages of the chain from donation to transplantation or disposal, are suitably qualified or trained and competent, and to develop continuous education and specific training programmes for such personnel in order to maximise the required skills. The important role of the donor coordinator or co-ordination team, appointed at hospital level, should be recognised as crucial for improving not only the effectiveness of the process of donation and transplant, but also the quality and safety of organs to be transplanted. Likewise, certain medical activities in procurement organisations, such as donor selection and evaluation, should be performed under the advice and/or guidance of a qualified medical specialist/adviser [11].

i. A follow-up system for recipients and living donors that allows evaluation of outcomes. This is a prerequisite for quality improvements and for providing a means to stimulate and motivate the professionals involved. In all circumstances, the evaluation system (local, regional, national), and basic follow-up should include primary non-function, delayed graft function, re-transplantation and death-related/adjusted survival rates (graft and patient) [5].

j. The implementation of quality assurance programmes (QAPs) or QIPs in the deceased donation process in order to address performance and identify areas where improvement is possible. International organisations, such as the Council of Europe and the European Commission, have recommended establishing and promoting a QAP/QIP in every hospital where there is a potential for organ donation. These programmes should include access to and training on a specific methodology of QIP and should also ideally be compatible at national or international level to adequately allow for comparison of the results obtained and to adopt the most appropriate measures for improving organ donation [12].

k. Harmonisation of regulatory rules and controls worldwide should be developed, in order to enhance the safety and quality of transplants.

For further details about the recommendations and regulations in the donation and transplant field at international level, see Chapter 1, §1.5.

Note that, with the transposition of Directive 2010/53/EU into national laws, some of these principles are now mandatory requirements in EU member states and EEA countries, while some others remain fully under the competence of the member states. Nevertheless, all these principles remain crucial recommendations.

17.5. Quality management in organ donation

Implementation of a quality system in an organ procurement organisation will enable the achievement of four key objectives:

a. To ensure the quality and safety of the organs to be obtained and transplanted, minimising disease transmission to the recipient and ensuring that all possible risks are known and can be evaluated for the best risk–benefit analysis before transplantation.
b. To guarantee that the entire process is carried out ethically and legally, and is medically correct according to best medical practices and in compliance with legislation and ethical codes, including protection of living donors and prevention of commercial abuses.
c. To ensure good documentation and transparency throughout the process, from donation to transplantation, allowing full records and traceability of the entire process.
d. To establish a system of continuous improvement that will allow the improvement of outcomes by increasing the numbers both of identified possible organ donors (and their transition to utilised organ donors) and of organs transplanted, by improving the quality of life/survival of living donors and recipients, and by meeting other defined criteria.

In the context of organ donation, some aspects have been identified which need work to improve quality, such as the development, implementation and evaluation of QAPs/QIPs [12-13], of best practices [14] and of quality indicators (QIs) [15-16]. Quality criteria, also called 'best clinical practice' or 'good clinical practices', set standards that normal healthcare practice has to meet if it is to be considered as good-quality practice.

As mentioned earlier, the Council of Europe has recommended that all healthcare providers (represented by hospital, regional or national management structures) have a QAP/QIP system that allows monitoring of quality parameters at each of these organisational levels and the adoption of the most appropriate measures to improve organ donation (such as allocating resources, appointing programme officers, stimulating the activities of key actors) [12]. Appropriate standards must be defined at each level in order to compare the results with those of other regions or countries and facilitate the identification of aspects for improvement [13, 15, 16].

Two projects funded by the European Commission – Dopki and Odequs – have focused on quality management in organ donation (see §17.5.2.2). The Dopki project (Improving the Knowledge and Practice of Organ Donation, 2006-09) was developed by a consortium of 12 European transplant organisations with the objective of improving organ donation rates. The project produced indicators to be used to benchmark organ donation potential and provided some general recommendations that could be used by European healthcare policy makers as a basis to construct QAPs in the deceased donation process. This kind of programme is an essential internal tool for countries that establish common definitions and it can be used to make international comparisons [13]. The Odequs Project (Organ Donation European Quality System, 2010-13), involving experts from 16 European countries, developed a quality system for the donation process which defines a methodology for evaluating organ procurement performance that can be used at hospital level [15]. The project identified 123 quality criteria and developed 31 relevant QIs in the three types of organ donation – after brain death (DBD), after circulatory death (DCD) and from a living donor (LD) – regarding all three aspects of donation services: structure, procedures and outcomes [16].

Any of the quality management models mentioned at the beginning of the chapter could help to achieve the objectives cited when applied to the process of organ donation in hospitals or donor-procurement organisations.

To facilitate detailed description of the contents of this section, we use the basic outline of the ISO model, given its wide diffusion at international level. The ISO model is a quality management system based on processes. The different processes that take place in the organisation must be identified and classified into three large groups: strategic, operational and support. We analyse in a structured way the quality conditions that should be met in the different key activities of the donation process.

17.5.1. Strategic processes

Strategic processes allow us to define and deploy the policies, strategies and goals of the procurement organisation. These processes help us to specify what we are doing, why we are doing it and how we are doing it. This group includes two main aspects:

a. management issues: legal framework, functional organisation and personnel,
b. professional issues: education, continuing professional development, training and research.

17.5.1.1. *Organisational issues: legal framework, functional organisation and personnel*

Procurement organisations for both living donation and deceased donation must be authorised

and/or accredited by the HA competent to carry out these activities [5, 16].

Some steps of the *post mortem* organ donation process, such as the declaration of death, the approach to the family and the organisational aspects, must be undertaken and properly documented according to the laws of the country concerned [5].

Adequate resources must be made available for identifying possible organ donors and for the entire donation process. There must be sufficient, suitably qualified personnel to carry out all tasks. Every donation team or group in charge of organising the donation process should consist of enough members to ensure that donation activities can be carried out 24/7 [5, 14, 16].

All procurement organisations should include a donor co-ordinator (also called transplant co-ordinator, key donation person or donation specialist) and a medical specialist/adviser, who may or may not be the key donation person [5]. The donor co-ordinator (DC) should be responsible for developing a proactive donor-identification programme and for organising and monitoring the entire donation process and donor programme at the hospital, along with a documented delegate who takes over this responsibility in their absence (see §1.3.6) [5, 11]. The ideal profile of the DC would include motivation, dedication, work capacity and good communication skills [14]. The DC should report directly to the head/director of their institution [16].

The procurement organisation should have an organisational chart in place showing the hierarchical structure of the organisation and clear delineation of tasks and responsibilities. The position of the DC and delegate, the quality function within the operations and all staff involved in the provision of the service should be highlighted.

All members of staff, including the DC and delegate, should have specific duties, including reference to legislative requirements recorded in written and up-to-date job descriptions, and adequate authority to carry out their responsibilities. Job descriptions should be signed and dated by the incumbent. Tasks and responsibilities assigned to an individual should be clearly defined, understood and documented.

Every donor hospital should have an office for the exclusive use of the donation team. It should be identified by a sign, secure and equipped with means of communication (telephone, fax, internet) [16].

In addition, the organisation should include an independent head of quality management, independent in the sense that this person is not directly involved in the organ donation programme [1-4].

Depending on the organisation of each national health care system, this schema may need adjustments locally without significant deviation from the key issues of the recommendations mentioned above.

Importantly, organ donation activities must be supported, and their quality checked, by the healthcare provider and/or regional management.

17.5.1.2. *Education, continuous training and research*

Personnel involved in procurement should receive specific initial training under a programme certified by the corresponding national/European agency, organisation or professional association (for instance, the Board of Transplant Coordination certification of the UEMS/European Union of Medical Specialists – Transplantation Section, which operates in close collaboration with the European Society for Organ Transplantation[1]), the training should be appropriate to the duties assigned to them and they should participate regularly in continuing medical training courses on specific topics related to donation [11, 14, 16].

Regarding the surgical aspects of organ procurement, including the ability to assess donor suitability and the ability to recover multiple organs, it is recommended that participating surgeons be certified as transplant specialists (for instance, by UEMS, the European Board of Transplant Surgery[2]). Equivalent national systems would fulfil this recommendation too.

The effectiveness of all training programmes should be monitored by regular assessment of the competence of personnel. Training should be documented and training records should be kept. Training plans including induction, refresher and continued training must be developed for individual staff members and a defined ongoing competency assessment programme must be implemented for relevant personnel.

Personnel must also be trained in quality principles relevant to their duties and in the broad ethical and regulatory framework in which they work.

Each donation team should also define objectives for research projects, conference communications and scientific publications relating to donation [16].

1 https://uemssurg.org/divisions/transplantation/transplant-coordination.

2 https://uemssurg.org/divisions/transplantation/transplant-surgery.

17.5.2. Operational (or key) processes

These processes are linked directly to the realisation of the service; they form the operational core of our activity and add value. In our case they represent all the processes related to the effective obtaining of donors and organs (and tissues) for transplantation, and include work instructions, process checklists and protocols, escalation processes, case review meetings, evaluation processes, the change management process and data collection processes.

17.5.2.1. *Donation process – implementation of protocols and checklists*

The following aspects of the donation process should be included in the protocols and monitored [5, 16, 17]:

a. Donor identification and referral, including a systematic approach to evaluating the potential for organ donation in every end-of-life care pathway (DBD or DCD) and the necessity of referring to the donation team all possible donors, whatever their medical situation (age, past medical history, etc.). The donation team should also monitor the progress of each possible donor in ICUs on a daily basis [18, 19] (for further information, see Chapter 2).

b. Donor assessment and donor selection. All potential donors should be carefully assessed by the donation team in order to establish their suitability for organ donation; they should be assessed and selected according to agreed principles and/or national regulations (see chapters 6 and 7).

c. Death determination by both neurologic and circulatory criteria. Each hospital should have developed and implemented SOPs and standard documentation (protocols) to permit and regulate brain death and circulatory death declarations in adults and children according to the legal framework. Every potential donor should be promptly diagnosed following comprehensive, accurate and documented methodology (see chapters 3 and 12).

d. Donor treatment/maintenance should be performed in an ICU with adequate means and under the supervision of an intensive care specialist according to best clinical practices; checklists and guidelines for donor maintenance should be available and updated regularly [20] (see Chapter 5).

e. Family support and granting of consent, according to the regulations of the relevant member state [19] (see Chapter 4).

f. Operating theatre organisation, organ procurement and organ sharing. There should be a clearly defined procurement protocol (including obligatory documentation) and every hospital should follow the established rules for organ sharing at a regional or national level (see Chapter 11).

g. Organ preservation, packaging, labelling, organ transport (in-hospital, inter-hospital) and logistics. There should also be procedures for packaging of organs, with the necessary biological samples and documentation, in shipping containers (e.g., as in Article 8 of Directive 2010/53/EU), and for transport of organs and biological specimens; traceability and donor anonymity should be guaranteed; logistical and auxiliary services for transport of organs and biological specimens should be ensured 24/7 (including air transport, if necessary); during the entire process, all containers should be clearly labelled and there should be instructions concerning the type and method of labelling (see Chapter 11).

h. Communication procedures with the national/regional co-ordination system should be in place, and the donation team should notify each potential donor in real time.

i. Development of training, promotional and educational activities to spread the culture of donation and transplant, directed at healthcare professionals, donor unit personnel (physicians and nurses) and the community (e.g. school activities, public conferences and mass media).

j. Archiving of documents, in accordance with national legislation.

After each donation operation, a debriefing should take place with the donation team and all personnel involved in the operation (from the identification to the recovery, packaging and delivery of organs) in order to improve the process quality [16].

17.5.2.2. *Quality indicators (or key performance indicators/KPIs)*

A quality system should periodically measure and evaluate relevant aspects of healthcare by means of quality indicators (QIs). QIs are measurements that indicate the presence of a phenomenon or event and its intensity. The objective of monitoring is to identify problems or situations that could be improved or deviations from standard practice; indicators act as alarms, warning us about possible anomalies [21].

Any set of indicators should ideally include a combination of the three types of evaluation:

a. structure: resources and organisation of care (e.g. protocol, circuit);
b. process: the way care is provided (e.g. adherence to protocol, efficacy);
c. results: achievement of goals (e.g. mortality, adverse events and reactions, nosocomial infections).

In order to have sufficient information to determine the level of quality of the service, a selected group of indicators has to be monitored.

Table 17.1. **The most important indicators applied in the DOPKI pilot (key indicators in blue)**

a. Indicators of the potential for deceased organ donation	
Of the number of deaths:	
Brain deaths (possible and confirmed) / Hospital deaths	**× 100**
Brain deaths (possible and confirmed) / ICU deaths	**× 100**
Brain deaths (possible and confirmed) / Number of persons who died within the hospital whose primary and/or secondary diagnosis contained at least one of the ICD codes [11] representing diseases potentially progressing towards a situation of brain death	× 100
Brain deaths (possible and confirmed) / Number of persons who died within the ICU whose primary and/or secondary diagnosis contained at least one of the ICD codes [11] representing diseases potentially progressing towards a situation of brain death	× 100
b. Indicators of areas for improvement in the deceased donation process	
Of the number of brain deaths (possible and confirmed):	
Brain deaths not referred / Brain deaths	× 100
Brain deaths lost because of medical contraindications to organ donation / Brain deaths	× 100
Brain deaths lost because of maintenance problems / Brain deaths	× 100
Brain deaths lost due to refusal for organ donation / Brain deaths	× 100
Brain deaths lost due to coroner refusal for organ donation / Brain deaths	× 100
Brain deaths lost due to organisational problems / Brain deaths	× 100

$$\frac{\text{Brain deaths lost for other reasons}}{\text{Brain deaths}} \times 100$$

Of the total number of families approached and judicial requests to proceed with organ donation:

$$\frac{\text{Number of families who refused organ donation}}{\text{Number of families approached to request organ donation}} \times 100$$

$$\frac{\text{Number of coroner refusals of organ donation}}{\text{Number of judicial requests for organ donation}} \times 100$$

c. Indicators of global effectiveness in the deceased donation process

Regarding the number of deaths:

$$\frac{\text{Actual donors}}{\text{Hospital deaths}} \times 100$$

$$\frac{\text{Actual donors}}{\text{ICU deaths}} \times 100$$

$$\frac{\textbf{Actual donors}}{\textbf{Brain deaths (possible and confirmed)}} \times 100$$

Other

$$\frac{\text{Multiple-organ donors}}{\text{Actual donors}} \times 100$$

$$\frac{\textbf{Utilised donors}}{\textbf{Actual donors}} \times \mathbf{100}$$

$$\frac{\textbf{Organs procured}}{\textbf{Actual donors}} \times \mathbf{100}$$

$$\frac{\text{Organs utilised}}{\text{Actual donors}} \times 100$$

$$\frac{\textbf{Organs utilised}}{\textbf{Utilised donors}} \times \mathbf{100}$$

Actual donor: A donor from whom at least one organ has been procured for the purpose of transplantation.
Utilised donor: An actual donor from whom at least one organ has been transplanted.
Source: [13].

In relation to organ donation, two sets of indicators have been described which, although they complement each other, are quite different in terms of philosophy, objectives and methodology. One set of indicators was published in the *Guide of recommendations for quality assurance programmes in the deceased donation process*, developed by the DOPKI project (Improving the Knowledge and Practice of Organ Donation, 2006-09) [13], and the other set was developed in the ODEQUS project [15-16].

Table 17.2. **Quality indicators applied in the ODEQUS project**

Living donation	**Applies to**	**Type**	**Standard**
1 Approval for living donation from a council*	LD	process	100 %
2 Participation of the centre in a living donor registry	LD	process	100 %
3 Identification of potential living kidney donors	LD	outcome	20 %
4 Long-term follow-up of living donors	LD	process	100 %
5 Evaluation of potential living donors	LD	outcome	80 %
Deceased donation	**Applies to**	**Type**	**Standard**
1 Donation process procedures	DBD/DCD	structure	100 %
2 Proactive Donor Identification Protocol	DBD/DCD	structure	100 %
3 Donation team full-time availability	DBD/DCD	structure	100 %
4 Donation team members with ICU background	DBD/DCD	structure	50 %
5 Dedicated time Key Donation Person	DBD/DCD	structure	100 %
6a Documentation of key points of the donation process	DBD/DCD	structure	100 %
6b Documentation of reason for non-donation	DBD/DCD	process	100 %
7 Patient/ family consent	DBD/DCD	outcome	90 %
8 Identification of all possible donors in ICU	DBD	process	75 %
9 Uncontrolled in-hospital DCD donor identification	DCD	process	100 %
10 Controlled DCD donor identification	DCD	process	100 %
11 Existence of controlled DCD donation protocols	DCD	structure	100 %
12 Referral of possible DBD donors	DBD	process	100 %
13 Discarded organs documented	DBD/DCD	process	100 %
14 Evaluation of brain-dead donors	DBD	process	100 %
15 Donor management	DBD	process	90 %
16 Unexpected cardiac arrest	DBD	outcome	3 %
17 DCD organ donor preservation	DCD	process	85 %
18 Seminars on organ donation	DBD/DCD	process	≥ 1
19 Documentation of evaluation of potential donors	DBD/DCD	process	100 %
20 Brain death identification	DBD	outcome	50 %
21 Conversion rate in DBD donors	DBD	outcome	75 %
22 Conversion rate in uncontrolled DCD donors	DCD	outcome	85 %
23 Conversion rate in controlled DCD donors	DCD	outcome	90 %
24 Kidneys transplanted from uncontrolled DCD donors	DCD	outcome	80 %
25 Kidneys transplanted from controlled DCD donors	DCD	outcome	90 %

DBD: donation after brain death; DCD: donation after circulatory death; ICU: intensive care unit; LD: living donor.
*A council is an *ad hoc* multidisciplinary group that evaluates the LD to ensure safety and best outcome for both patients, following the principles laid down by the transplant centre's ethical committee.
Source: Project ODEQUS (Organ Donation European Quality System) [16].

17.5.2.2.1. Quality indicators developed by the DOPKI project

These recommendations on QIs are based on the experience and knowledge acquired in the DOPKI project, particularly on the state of the art in QAP in the deceased donation process in each of the participating countries [22-26]. This project included group discussions on specific aspects and the pilot experience which took place in a group of 30 volunteer hospitals in 12 European countries, with the aim of validating the pre-agreed methodology.

QIs developed by the DOPKI Project were grouped as follows [13]:

a. Indicators of the potential for deceased organ donation.
b. Indicators of areas for improvement in the deceased donation process.
c. Indicators of global effectiveness in the deceased donation process.

Indicators developed during the DOPKI pilot experience are shown in Table 17.1. Out of those, six key indicators were identified (highlighted in blue in the table).

The DOPKI consortium stated that, in applying this set of indicators to specific hospitals, certain hospital variables or factors need to be taken into account

that may justify the existence of differences between hospitals that, at least on the surface, seem to have similar characteristics. Among such factors, the following must be considered: the epidemiology of diseases concerned and hence the number of persons dead as a result of a devastating brain injury within a hospital or ICU; the presence of neurosurgical facilities in the hospital; the number of hospital and ICU beds; the ICU workload (the greater the workload in an ICU, the lower the potential for *post mortem* organ donation) or differences in age and ethnicity between populations, which could have an influence on some aspects (e.g. consent rate) [13].

A QAP in the deceased donation process is primarily a self-assessment of the whole process of organ donation, jointly performed by intensive care specialists and donor co-ordinators in every hospital. It involves a systematic review of all medical records of patients who have died in ICUs, and possibly in other similar units, being performed on a regular basis in order to analyse any undetected potential donors and establish means for improvement. After implementation of the self-assessment, the programme should be complemented by regular external audits performed by experts from other hospitals, regions or countries, in order to further improve the process and provide greater transparency.

For clinical use of this group of indicators, it is important to note the following [13]:

a. Dopki recommendations are exclusively focused on the process of DBD.
b. The groups of indicators form part of a QAP implemented at national/regional level and usually managed by the corresponding transplant organisations so, to a certain extent, they may be mandatory.
c. Reference values (national or regional) should be available with which to compare the results obtained after implementing the indicators, particularly taking into account the socio-demographic characteristics, economic situation and available healthcare structure in the respective area.
d. By the very nature of the QAP, its scope is focused almost exclusively on the actions of individuals and outcomes, focusing less on the analysis and evaluation of processes and on the implementation of improvement plans.

17.5.2.2.2. Quality indicators developed by the Odequs project

The Odequs consortium developed a quality management system to assess the performance of organ procurement at hospital level. The specific objectives were to identify best practices in the three different types of organ donation (DBD, DCD and LD) and to design QIs to assess the organisational structures, clinical procedures and outcomes. Indicators developed were tested in selected hospitals in 12 European countries to assess their feasibility and usefulness. Healthcare workers were trained beforehand on how to use the QIs, checklists and auditing procedures [15].

The main fields considered in assessing the organisational structures were:

a. legal framework,
b. accreditation and certification,
c. organisation,
d. human and material resources,
e. education,
f. research.

In terms of clinical procedures and outcomes, the main aspects assessed were:

a. donor identification,
b. clinical evaluation,
c. death diagnosis,
d. donor maintenance,
e. family/personal consent,
f. organ viability,
g. surgical procurement/preservation,
h. number of donors/organs/transplants.

From the analysis of best practices in organ donation conducted by the 16 donation experts, a quality criteria list of 123 items was compiled on the basis of expert opinions, literature review and evidential research. Once they had received specific training designed for this task, the same group of experts developed and agreed on a list of 31 key quality indicators based on the most important quality criteria previously identified [16]. The list of QIs developed by Odequs is shown in Table 17.2, specifying the type of organ donation where applicable (LD, DBD and/or DCD), type of indicator (structure, process or outcome) and level of the standard.

All the indicators developed have the same structure. As examples, Table 17.3 and Table 17.4 show two QIs of deceased donation: Documentation of reason for non-donation, valid for the DBD/DCD population (Table 17.3); and Controlled DCD donor identification (Table 17.4). Each one of the QIs includes the following data [16]:

a. name of the indicator,
b. justification (why the indicator is relevant and of practical use),

Table 17.3. **Deceased Donation indicator 6b in the Odequs project: documentation of reason for non-donation**

Name	6b. Documentation of reason for non-donation
Justification	Proper documentation of the cause of non-donation ensures that it will be possible later to review and analyse donor losses. This is the basis that will enable continuous improvement.
Strength of evidence	Recommendation C
Dimension	Appropriateness
Formula	$\frac{n_1}{n_2} \times 100$ where: n_1 = number of referred failed donors in whom the cause of no donation is properly documented n_2 = number of referred failed donors
Explanation of terms	Donor referral: see glossary (Appendix 2) Possible donor: see glossary (Appendix 2) Failed donor: Possible donor who did not become an actual donor. Cause of non-donation properly documented: if in the records of the patient there is a note stating the cause by which the patient did not become an actual donor.
Population	All possible referred donors who did not become actual donors
Type	Process
Data source	Donation team records
Expected result	100 %
Comments	Note: in order to standardise the evaluation of causes of donor's loss the recommendation is to implement a closed list of possible causes.

Source: Project Odequs (Organ Donation European Quality System) [15].

c. strength of evidence (Recommendation A: consistent, good-quality patient-oriented evidence; Recommendation B: inconsistent or limited-quality patient-oriented evidence; and Recommendation C: consensus, disease-oriented evidence, usual practice, expert opinion, or case series for studies of diagnosis, treatment, prevention or screening),
d. dimension (characteristics of the healthcare in order to be considered good-quality care, e.g. effectiveness and appropriateness, efficiency),
e. formula for rate-based indicators,
f. clarification of terms (explanation or definitions of terms included in the formula that are ambiguous),
g. type (structure, process or outcomes),
h. data source (medical records or other clinical documents, direct observation, questionnaires, etc.),
i. expected results,
j. comments and bibliography (scientific soundness, face validity, reliability, references to literature regarding scientific evidence, etc.).

The feasibility of implementation of the QI should be assessed by two types of evaluation:

a. Internal audit, performed by a team from the same hospital.
b. External audit, performed by an outside team (national or international).

The Odequs Quality System can be summarised as follows:

a. Odequs is designed as a quality management system that incorporates regular monitoring of a series of QIs that will allow us to identify problems or situations that can be improved, with the commitments to take action at the time when the practice evaluated presents below-standard results, to discuss these results, to analyse the causes and to define and implement improvement plans (e.g. Shewhart PDCA cycle: Plan–Do–Check–Act, sometimes called PDSA: Plan–Do–Study–Act).
b. It is focused on evaluating the three types of donation: LD, DBD and DCD.
c. It covers all three aspects of donation services: structure, procedures and outcomes, and therefore provides a broader evaluation.
d. It is a proactive approach to improvement of healthcare processes and systems that will lead to improved processes and outcomes, rather than improving the outcomes alone.

Another EU-funded project should be mentioned here: the Accord Joint Action (2012-15) has a work package (Work Package 5) focused on deceased donation and more specifically on collaboration between ICUs and donor co-ordinators. It applies the PDSA methodology, as a rapid improvement tool based on a common framework and the self-assessment of hospitals involved, in 15 countries all over Europe [27].

17.5.3. Support processes

These are processes that offer support to operational processes. These processes do not contribute directly to what the customer/patient wants/needs but they do help the key processes to achieve it, and they include:

Table 17.4. **Deceased Donation indicator 10 in the ODEQUS project: cDCD donor identification**

Name	10. Controlled DCD donor identification
Justification	Organ donation is a priority programme for the majority of a country's health systems. DCD donation has proved to be an adequate supply of organs for transplantation and can represent 10 %-20 % of the total number of organs available. These data confirm the importance of identifying all patients who undergo WLST in ICUs and who could become DCD donors.
Strength of evidence	Recommendation C
Dimension	Effectiveness
Formula	$\frac{n_1}{n_2} \times 100$ where: n_1 = number of patients who underwent WLST, were apparently medically suitable for organ donation AND were correctly identified and referred n_2 = number of patients who underwent WLST and were apparently medically suitable for organ donation
Explanation of terms	WLST: withdrawal of life-sustaining therapies, in an ICU patient. Identified and referred: the patient is reported to the donation team (or transplant centre) as soon as the decision to withdraw life-sustaining therapies is made by the ICU medical team. Apparently medically suitable for organ donation: at the moment of the decision to withdraw life-sustaining therapies it is not known if the patient has a malignancy (see Chapter 9 for details), sepsis with multiorgan failure or symptomatic HIV infection.
Population	All patients admitted to the ICU to whom WLST is applied during the period studied. Exclusion criteria: only withdrawing (not withholding) life support is considered.
Type	Process
Data source	Medical records and donation team referral registry
Expected result	100 %
Comments	Note: In order to ensure the feasibility of the indicator the recommendation is to document accurately the time when WLST is decided, the time when it is performed and the time of death. The definition of Potential DCD Donor in the Critical Pathway includes the statement 'the cessation of circulatory and respiratory functions is anticipated to occur within a time frame that will enable organ recovery'. As the accuracy of the different systems to predict such an event is low, we have decided to exclude this point from the indicator. This eliminates subjectivity and improves its accuracy.

DCD: donation after circulatory death; ICU: intensive care unit; WLST: withdrawal of life-sustaining therapy.

Source: Project ODEQUS (Organ Donation European Quality System) [15].

a. audits, quality evaluation and outcomes,
b. documentation and registries,
c. traceability,
d. investigation and reporting of non-conformance: vigilance system,
e. risk assessment and mitigation,
f. change control,
g. complaints and recalls,
h. premises, equipment, materials and contractual arrangements.

Each of these support processes is discussed below, in the rest of section 17.5.

17.5.3.1. *Audits, quality evaluation and outcomes*

An audit is a documented review of procedures, records, personnel functions, equipment, materials and facilities to evaluate adherence to quality criteria and national/governmental laws and regulations. During an audit, performance is reviewed to ensure that items that should be carried out in terms of quality management are being done and documented; if this is not the case, it provides a framework to allow improvements to be made.

Auditing is an essential tool to ensure ongoing improvements, and may be performed in different ways:

a. Self-assessment: donation team personnel review each step in the process.
b. Internal audit: performed by the organisation's own quality personnel, who must be qualified for auditing.
c. External audit: carried out by independent bodies, often designated as approved or by competent authorities; external audit is often required for accreditation or licensing purposes.

Following international recommendations, as a complement to self-assessments, each procurement organisation should perform an annual external audit of the organ-donation process and should implement corrective measures when needed [12, 14, 16].

17.5.3.2. *Documentation and registries*

Documentation must enable all steps and all data affecting the quality and safety of the organs to be checked and traced, from donor to recipient and vice versa. Written documentation enables/facilitates standardisation of the organ donation process and prevents errors that may result from oral communication. Where oral communication is necessary, audio recordings may be useful.

Documentation should be version-controlled,

be regularly reviewed and cover at least the following items:

a. A quality manual (a document that gives an overview of the quality-related activities of the procurement organisation).
b. SOPs, including documentation for all activities that influence the quality and safety of organs and tissues and cells, including the quality management system itself (e.g. document control, change control, recall, complaints, non-conformance, contractual arrangements; internal and external audits).
c. Records of performance of operations (e.g., donor selection, procurement reports, organ allocation).
d. Specifications.
e. Identification of risks and a risk-mitigation plan.
f. Other procedures (e.g., equipment validation, calibration, cleaning and maintenance).
g. Training and competency of personnel.

Documents should be approved by appropriate and authorised persons. Any alterations made to a record should be dated and signed.

Documents relating to the selection of donors, preparation and quality control should be retained for a minimum of 30 years after donation in EU member states, in accordance with Directive 2010/53/EU [5]. International and national regulations on data protection have to be taken into consideration. Data can also be stored in soft-copy form, for instance on computer or microfilm. Users should have access only to those categories of data for which they are authorised and for the purposes authorised.

A computerised record-keeping system ensures the authenticity, integrity and confidentiality of all records, but retains the ability to generate true paper copies. The hardware and software of computers should be regularly checked to ensure reliability. Computer programs should be validated before use. Only authorised persons should make changes to computerised systems and any such changes should be validated before use. In addition, appropriate hardware and software should be in place to guarantee secure back-up, data protection and logging of user activities. Hospitals and other facilities should have an alternative record-keeping system that ensures continuous operation in the event that computerised data are not available.

17.5.3.3. *Traceability*

In accordance with the traceability system implemented in each country (or internationally, if applicable), each procurement organisation must maintain records that allow the location and unequivocal identification of each organ at any stage in the chain from donation to transplantation or disposal. The system must fully respect the confidentiality of both donor and recipient, and data security measures should be in compliance with European Union and national provisions.

Each donor and the associated organs, tissues and cells must be assigned a unique identifier that may also serve as a lot/batch number to identify the material during all stages, from collection to distribution and utilisation. This unique number should be used to link the donor to all tests, records, grafts and other material (e.g. preservation solutions, preservation devices) and, for tracking purposes, to the recipient. Records should include: identification, clinical and laboratory evaluation of the donor; verification of the conditions under which the material was procured, processed, tested and stored; and the final destination and recipient of the donor material. Records should indicate the identities of personnel involved in each significant step of the operation and the dates and time of those steps [5].

There should be regular audits of the system to ensure traceability as part of the internal audit system.

17.5.3.4. *Investigation and reporting of non-conformance: vigilance system*

Non-conformance includes deviations, incidents, accidents and serious adverse reactions and events (SAR/SAE) in relation to organ donation processes.

Organisations involved in the donation–transplantation process should record and document incidents and deviations from established procedures and specifications. Procedures should be in place to identify the problems to be corrected, and to inform the relevant authorities as appropriate according to the national vigilance system [5]. For further details of the biovigilance system, see Chapter 16.

Priority should be given to the investigation and reporting of incidents with a demonstrated or potential risk to cause serious adverse reactions, for example, unexpected transmission of an infectious or malignant disease from a donor to a recipient or any incident during the process that might lead to a problem in a recipient. Unexpected infections or malignancies in recipients must be reported without delay, as early warning may facilitate interventions or prophylactic measures that could mitigate adverse outcomes in other recipients of organs or tissues from the same organ donor (possibly in another unit, region or country). For this reason, where it is con-

sidered that a non-conformance other than an SAR/SAE may have the potential to impact another procurement organisation or transplantation centre, the details of the non-conformance should be formally communicated to them so that they may undertake such investigations and actions as they may consider necessary.

All reported and documented incidents, deviations, events and reactions should be carefully discussed and analysed to identify possible areas of improvement and to avoid repetition. The effectiveness of corrective and/or preventive actions should be monitored and assessed, in line with quality risk management principles.

Open reporting of errors and incidents should be encouraged for improvement in practices to be shared among all institutions involved in all Council of Europe member states.

17.5.3.5. *Risk assessment and mitigation*

Donor selection, procurement, manipulation and distribution of organs should be subject to a comprehensive risk assessment [5]. Where appropriate, a process-flow diagram listing all relevant steps, processes, re-agents, tests and equipment can form the basis for this assessment exercise. Risk-mitigation strategies should then be developed (specific protocols) to protect transplant-associated products, patients, personnel, and the process itself and other linked or related processes. For further details about the communication of risk, see Chapter 19.

For example, risks might derive from: donor selection and screening, procurement procedures, preservation and transport, biological properties of procured organs, the absence of standardised quality control tests or the use of potentially infective materials.

17.5.3.6. *Change control*

Arrangements should be in place for the prospective evaluation of planned changes, and their approval prior to implementation, taking into account regulatory notification and approval where required. Any changes to the processes, materials, equipment and facilities that may impact the quality and safety of organs should be reflected in documentation and, where relevant, written procedures. After implementation of any change, an evaluation should be undertaken to confirm that the quality objectives were achieved and that there was no unintended deleterious impact.

Where temporary and time-limited changes are implemented, provisions should be in place to ensure and verify the changes are reversed as appropriate.

17.5.3.7. *Complaints and recalls*

All complaints and concerns about any aspect from donation to transplant – from any source, including: donating hospitals and transplantation centres, patients, staff, third party health professionals, transplantation centres in other jurisdictions and third-party service providers (material that may be in contact with the donor or the organs, like pharmaceutical products, preservation liquids, laboratory re-agents, etc.) and if the complaints or concerns may be potentially harmful to the recipients or may represent a health public problem – should be documented, carefully investigated and dealt with in a timely manner and immediate actions taken as required.

Effective written procedures must exist for recalling defective/potentially harmful products [28]. These written procedures must encompass any review procedures that may be necessary. The procedures should be communicated to the end users. A mechanism for appropriate review and assessment of actions taken to address complaints should be established.

17.5.3.8. *Premises, equipment, materials and contractual arrangements*

Premises and equipment must be designed, located, constructed, adapted and maintained to suit the operations to be carried out. Their layout and design must aim to minimise the risk of errors and permit operations to proceed in an orderly sequence, and should allow for effective cleaning and maintenance in order to avoid any adverse effect on the quality and safety of the organs intended for transplantation.

a. *Premises*

Premises for each step in the transplant process should be specified (e.g. where the donation process will be carried out, allowing for confidential, personal interviews) and comply with existing recognised regulations.

Donor selection should be performed on the premises of the donating hospital where the donation process is carried out. The procurement and transplantation of organs must take place in operating theatres which are designed, constructed, maintained and operated in accordance with adequate standards and best medical practices.

All laboratory investigations (e.g. tissue typing for human leukocyte antigens and cross-matching, screening for infections, pathology investigations) should be done in certified laboratories, using methods and techniques that

are certified and quality-controlled by internal and external methods.

All outsourced activities should be handled with attention to ensure that all changes are communicated and managed.

Storage areas should be of sufficient capacity to allow orderly storage of the various categories of materials and components. There should be dedicated, secure and monitored areas for the storage of different types of organ. Storage conditions for organs and materials should be controlled, monitored and checked. Appropriate alarms should be present to indicate when storage temperatures fall outside acceptable levels in cases of donor material stored for further processing. Alarms should be regularly checked. SOPs should define the actions to be taken in response to alarms.

b. *Equipment*

There should be a controlled list of equipment utilised by the procurement organisation. All critical equipment that might influence the quality and safety of the organ should be identified and validated.

Adequate and standardised equipment for the entire organ retrieval process should be available 24/7 (surgical equipment, preservation fluids, transport boxes etc.) [15].

All equipment that might influence the quality or safety of transplant-associated products should be designed, validated and maintained to suit its intended purpose and to minimise any hazard to donors, recipients or operators. Maintenance, monitoring, cleaning and calibration should be documented, and these records should be appropriately maintained.

c. *Materials*

Detailed specifications of re-agents and other materials that might influence the quality or safety of transplant-associated products are required. Only materials from qualified suppliers that meet the documented requirements should be used. Manufacturers should provide a certificate of compliance for every lot/batch of such materials.

Equipment and materials should conform to international standards and European and national licensing arrangements, where these exist.

Inventory records should be kept for traceability and to prevent use of materials after their expiry date. Deviations in the quality and performance of equipment and materials should be investigated and documented promptly [28]. The outcomes of these investigations should be reported in a timely manner to the person responsible and corrective actions taken. For substantial deviations, a notice should be sent to the manufacturer and, where appropriate, reported to the HA.

d. *Contractual arrangements*

Where steps influencing the quality or safety of organs intended for transplantation, i.e. prescribed activities, are outsourced to a third party, there should be a contract or agreement in place that describes the roles and responsibilities of all parties in maintaining the quality chain and the quality requirements for the service provided.

Arrangements relating to procurement services independent of the procurement centre, testing laboratories, processing, storage, transport companies, or any service provided by/for an organisation in another country, should be documented, and compliance with professional standards should be ensured by all parties involved.

17.6. Quality management in organ transplantation

The characteristics of transplantation, regardless of organ type, make this process a model of multidisciplinary care. The complexity, involvement of different specialties, levels of care and speed required in transplant situations make the combination of co-ordination and quality management essential in this area of healthcare [29].

Multiple variables affect organ transplantation (type of organ transplant, living or deceased donors, urgent or elective transplant etc.), and a global approach needs to be taken for the transplant process. In general, the term 'transplant/transplantation centre' will be used for all those health centres that, by fulfilling the established requirements, are duly authorised to perform some type of organ transplant.

Following a similar pattern to the previous section, the different quality criteria used for organ transplant are now reviewed under the following headings:

a. Organisational issues: legal framework, functional organisation and personnel
b. Education and continuous training
c. Transplant process: implementation of protocols and checklist

d. Quality indicators (or key performance indicators/KPIs)
e. Audits and quality evaluation
f. Documentation and registries, traceability, vigilance system, assessment and mitigation of risks, complaints and recalls, and resource management.

17.6.1. Organisational issues: legal framework, functional organisation and personnel

A transplant centre that performs any type of organ transplant, with organs from living and/or deceased donors, must have specific authorisation/ accreditation from the competent HA to conduct such activity [7].

As multidisciplinary functional units, transplant centres must have an establishment plan and an organisational structure with well-defined responsibilities and hierarchies in all areas of activity (medical, surgical, anaesthesia, nursing etc.). In all cases, functional management positions must be filled by physicians, nurses or other healthcare professionals who specialise in the area in which they work. Transplant centres must have specific and qualified personnel, in adequate and sufficient number so that each stage of the process can be carried out throughout the year, including the holidays and at all times of the day or night (24/7). There must also be an organisational and functional description of the different positions, which should include the profiles and qualifications required, and the activities corresponding to each functional group [29].

Transplant centres must have formal internal communication in the form of regular meetings in which all healthcare personnel concerned take part (and administrative personnel if necessary). In these meetings, key issues are analysed, such as:

a. Evaluation of recipients and consensual decision on transplant indication and patient prioritisation.
b. Information on and evaluation of morbidity of transplant centre patients.
c. Decisions made on treatment strategies for patients who are to be placed on a waiting list.
d. Follow-up of the status of patients on a waiting list.
e. Analyses of outcomes individually and compared with other groups or areas.
f. Other informational or organisational issues.

A record of the issues dealt with at each meeting should be kept in the form of minutes. The outcomes achieved by the programme should be made public on a regular basis (usually annually) with the publication of a report on healthcare, teaching and research activities.

Transplant centres should ensure that they carry out all the studies and procedures required, in accordance with the best medical practice, to guarantee the proper assessment of transplant candidates as well as their follow-up, either at the centre itself or through co-ordinating centres.

Also, transplant centres must have adequate physical space to suit the needs of the different areas for inpatients and outpatient follow-up visits.

In addition, transplant centre personnel should ideally also include an independent head of quality management, independent in the sense that this person is not directly involved in the organ donation programme.

Finally, according to Directive 2010/53/EU, member states in the EU shall ensure that the HA draws up and makes publicly accessible an annual report on activities of procurement organisations and transplant centres, including the types and quantities of organs procured and transplanted [5].

17.6.2. Education and continuous training

All staff involved in transplant activities must be suitably qualified or trained, competent to perform their tasks and provided with the relevant training [5]. Transplant centres must have an integration plan for new members of staff. This plan should include a description of the activities to be performed, the people responsible for training and mentoring at each stage and the duration of each stage, and the person responsible for validating the new staff member's training.

Surgeons involved in transplant activities should be encouraged to have specific training under a programme certified by the corresponding national/European agency, organisation or professional association (for instance, the European Board of Transplant Surgery, UEMS, mentioned before).

There should be a continuing professional development programme for all transplant centre personnel, based on properly identifying training requirements (through surveys, analysing adverse events, implementation of new treatments, techniques or procedures, etc.), which should be aimed at all transplant team members. All training activities should be properly documented, along with the training outcomes achieved, and the training's effectiveness in meeting the intended objectives.

17.6.3. Transplant process: implementation of protocols and checklist

The healthcare activities needed to perform transplants and the quality characteristics they entail must be described. The transplant process includes different stages, which should be properly monitored and written into procedures, protocols and checklists [29-31]:

a. Assessment and consensus, with the aims of assessing and agreeing whether a transplant is indicated for the patient and, if so, establishing a degree of urgency or priority and specific measures to optimise results. Transplant centres should have procedures and protocols that define and provide for the process of assessing a patient as a transplant candidate in order to ensure that it can be done in the shortest time possible. Subsequently, a multidisciplinary committee must decide whether to place a patient on the corresponding waiting list, leaving a written record of the decisions taken.

b. Management of patients on the waiting list for transplantation, which includes:

i. clinical, organisational and administrative criteria for placing patients on the transplant centre's waiting list and regional/national registries (as applicable);
ii. clinical monitoring of patients on the waiting list to enable optimisation of the overall situation of patients so that they arrive in the best condition possible for transplantation;
iii. establishing the level of priority for transplantation if warranted (based on the use of prognostic scores);
iv. appropriate allocation of grafts in accordance with donor–recipient eligibility;
v. communication: at this stage, patients (and in most cases their immediate family members) should be properly informed, both verbally and in writing, of the need for transplant, as well as the different phases of the process and the possible complications. Patients who agree must grant their consent to be placed on the waiting list as well as to undergo the transplantation when the time comes. There should be an educational programme for patients and families on the self-care required for getting into the best physical and psychological shape possible to prevent early and late post-transplant complications and on the importance of complying with the therapeutic regimen.

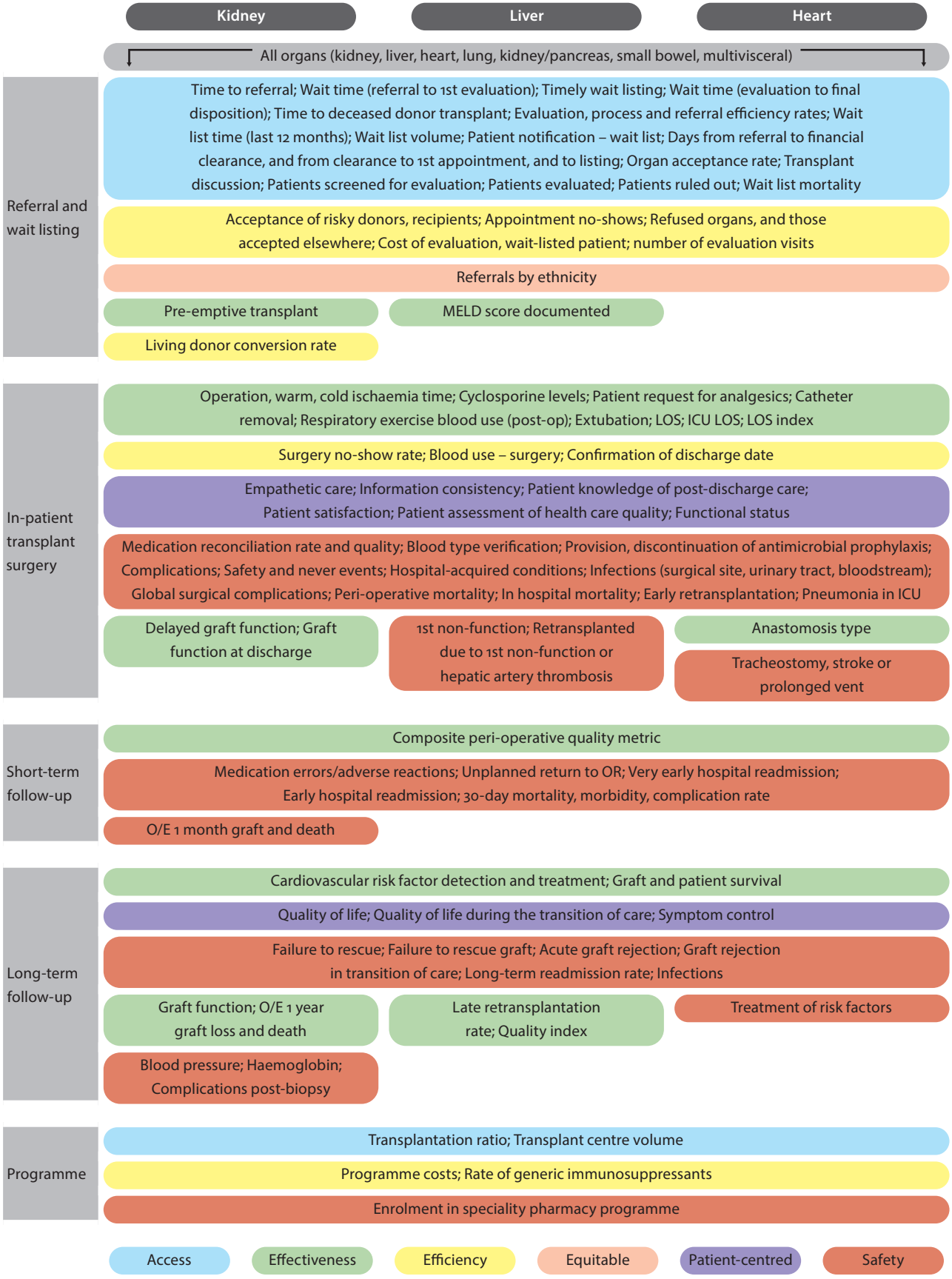
c. Peri-operative management of transplanted patients, which should be defined and written into protocols related to:

i. procuring donor organs of all types (living or deceased donors, in hospital or out of hospital, whether obtained by the centre's staff or by another centre) and ensuring the validity of the organ obtained;
ii. transportation of organs, including medical team, packaging, labelling, safety and integrity, identification, real-time monitoring of temperature and traceability of the organ during the process; the transport procedure should be validated and also performed by a qualified courier;
iii. correctly allocating organs to recipients;
iv. correctly preparing patients;
v. optimising the time to start of surgery and immediate results in transplanting the organ;
vi. transplanting the appropriate organ in line with the recipient's clinical characteristics;
vii. organising and co-ordinating the various professionals and units involved in order to ensure that needs are met and possible contingencies accounted for.

d. Post-transplant hospitalisation, which establishes the care required for patient recovery during the immediate and early post-operative periods after transplantation (in the ICU and the subsequent hospitalisation in the ward) and the monitoring of complications and optimisation of treatment to prevent organ rejection and immunosuppression-associated toxicity.

e. Post-transplant follow-up, which establishes appropriate clinical follow-up after hospital discharge in order to increase patient survival and quality of life and to minimise and/or anticipate the possible complications that frequently occur during the first year after transplantation: infections, acute drug-related toxicity, immune disorders, reactivation of the underlying disease, etc. For this post-transplant follow-up, there should be clinical protocols (e.g. follow-up visits, possible complications and treatment for them) and drug treatment (e.g. immunosuppression, use of antibiotics). The mid- and long-term follow-up of transplanted patients should also be ensured and continuously documented. This is crucial not only for the survival of the patient and their graft, but also more generally for the whole scientific community to learn from past transplants.

Figure 17.1. **Individual quality metrics grouped by domain of quality and mapped against the organ types where the metrics could apply**



Note: Only the kidney, liver and heart had organ-specific metrics (i.e., metrics that could not be applied to other organs). O/E, observed to expected; ICU, intensive care unit; LOS, length of stay; MELD, model for end-stage liver disease.

Source: adapted from Brett KE, *et al.* Quality Metrics in Solid Organ Transplantation: A Systematic Review, *Transplantation* (2018) [46].

17.6.4. Quality indicators (or key performance indicators/KPIs)

Some medical societies and working groups have defined their systems of transplant quality management by selecting various QIs that, when monitored, enable relevant aspects of the process to be measured and evaluated periodically [32-45]. These monitoring systems should include, as a minimum, the frequency of measurements, the system of collecting information and the person(s) responsible for collection (for further information, see §18.4.2).

A very complete and systematic review has identified 317 quality metrics in solid organ transplantation (of all types) that it has condensed into 114 QIs with sufficient detail to be measured in practice. Only for kidney, liver and heart transplants did the review find organ-specific QIs (i.e. metrics that could not be applied to other organs) [46]. Figure 17.1 summarises the QIs by grouping them by domain of quality (access, effectiveness, efficiency, equitable, patient-centred, safety) and period of care (referral and waiting list, inpatient transplant surgery, short-term follow-up, long-term follow-up, programme), and mapping them against the different organs to which they could be applied in future quality improvement initiatives.

Adopting a monitoring system based on indicators involves a commitment from the transplant centre to act – whenever the practice being evaluated gives results outside the established standards – by analysing the results obtained, identifying the causes and implementing improvement cycles where appropriate (e.g. the PDCA/PDSA cycles). It is crucial that all professionals involved keep this commitment in mind; otherwise the measurement becomes routine and has no utility in the management of the unit [21].

In order to avoid a too-exhaustive description, we have selected some indicators that could be used, with minor modifications and regardless of the type of organ transplant, to evaluate organ transplantation in the different phases discussed in section 17.6.3. Importantly, we can also incorporate indicators for the process of communication of risks (see Chapter 19).

The list of selected indicators is shown in Table 17.5, specifying definition of the indicator, formula used to calculate it and the type of indicator (process, structure or results). The standards to be met have not been included, because these differ for each type of organ transplant. More detailed information is available in references [32-46]. Importantly, a QI monitoring system should give feedback to those contributing through regular reports on quality and safety, thereby facilitating data-driven improvements in the processes of organ donation and transplantation.

Table 17.5. **Some quality indicators that can be used in deceased organ transplantation, regardless of organ**

Indicators for evaluation and consensus
Patients studied within 30 days of referral to the TC
• Definition: percentage of patients who have been evaluated (whether placed on the waiting list or not, after an evaluation) by the TC within 30 days of the appointment request. • Formula: Number of patients in a given period with study completed within 30 days of request for appointment for transplant evaluation/Number of patients in the same period referred for transplant evaluation × 100. • Type: Process
Quality of clinical report by doctor responsible for referring a candidate to the TC
• Definition: percentage of clinical reports that are full clinical reports (those specifying all the information contained in the evaluation checklist for the potential recipient) sent by the doctor responsible for referring a transplant candidate to the multidisciplinary committee. • Formula: Number of full reports sent to the committee in a given period/Total reports sent to the committee in the same period × 100. • Type: Process
Indicators of management of patients waiting for a transplant
Frequency of pre-transplant follow-up visits
• Definition: percentage of patients on the transplant waiting list who are seen in follow-up visits at a frequency of more than 60, 90 or 120 days (as applicable). • Formula: Number of patients on the waiting list seen in visits in a given period at a frequency of more than 60, 90, 120 days (as applicable)/Total number of patients on the waiting list × 100. • Type: Process
Mortality of patients on the waiting list
• Definition: percentage of patients excluded from the transplant waiting list because of death or disease progression. • Formula: Number of patients excluded from the waiting list in a given period (because of death or disease progression)/Total number of patients placed on the waiting list in the same period × 100. • Type: Outcome
Peri-operative indicators
Peri-operative mortality
• Definition: percentage of transplant patients who die during a period starting from the start of surgery and including the first 24 h post-transplant. • Formula: Number of deaths during the first 24 h of transplantation/Total number of transplant patients for the same period × 100. • Type: Outcome
Occurrence of primary graft failure
• Definition: percentage of transplant patients who develop 'primary graft dysfunction'. • Formula: Number of transplant patients in a given period who develop 'primary graft dysfunction' causing re-transplantation or death/Total number of transplant patients × 100. • Type: Outcome

Cold ischaemia time
- Definition: percentage of organs preserved by cold ischaemia (time between clamping blood supply to the organ in the donor and restoring blood supply in the recipient) for more than 3, 5, 10, 15 and 20 h (as applicable, depending on the type of transplantation).
- Formula: Number of organs in a given period preserved by cold ischaemia for more than 3, 5, 10, 15 and 20 h (as applicable)/Total number of organs transplanted in the same period × 100.
- Type: Process

Rate of non-transplanted organs with no justifiable objective reason
- Definition: percentage of non-transplanted organs after initial acceptance, with no justifiable objective reason (ideally, a histological study showing the impossibility of use).
- Formula: Number of non-transplanted organs after acceptance in a given period/Number of transplanted organs (based on applicable national acceptance criteria for deceased donors) in the same period × 100.
- Type: Outcome

Indicators of post-transplant hospitalisation

In-hospital mortality post-transplant
- Definition: percentage of transplant patients who die within the first 24 h/up to 30 days post-transplantation.
- Formula: Number of transplant patients who died within the first 24 h and up to 30 days post-transplantation/Number of transplant patients × 100, for the same period.
- Type: Outcome

Early re-operation rate
- Definition: percentage of transplant patients requiring a second, unscheduled operation in the subsequent 15 days because of a complication.
- Formula: Number of transplant patients in a given period undergoing re-operation in the first 15 days/Number of transplant patients in the same period × 100.
- Type: Outcome

Early mortality post-transplant with functioning transplanted organ
- Definition: percentage of transplant patients who die during hospitalisation post-transplant with a correctly functioning transplanted organ.
- Formula: Number of transplant patients who died during post-transplant hospitalisation with normal transplanted organ function/Number of transplant patients × 100, for the same period.
- Type: Outcome

Post-transplant follow-up indicators

Re-transplant rate
- Definition: percentage of re-transplants overall in the series of transplants (not valid in kidney transplantation).
- Formula: Number of re-transplants in a given period/Total number of transplants in the series × 100.
- Type: Outcome

Survival of transplant patients
- Definition: survival rate of transplant patients in the series at 1, 3, 5 and 10 years post-transplant.
- Formula: Number of transplant patients alive at the time of each threshold or analysis (1, 3, 5 and 10 years)/Number of transplant patients at the beginning of the period. Actuarial survival curves (Kaplan–Meier method).
- Type: Outcome

Graft survival
- Definition: overall rate of graft survival in the series of transplants at 1, 3, 5 and 10 years post-transplant.
- Formula: Number of functioning organs at the time of each threshold or analysis (1, 3, 5 and 10 years)/Number of grafts transplanted at the beginning of the period. Actuarial survival curves (Kaplan–Meier method).
- Type: Outcome

Mortality post-transplant with functioning transplanted organ
- Definition: percentage of transplant patients who die with a well-functioning transplanted organ.
- Formula: Number of transplant patients who died with normal transplanted organ function/Number of transplant patients × 100, for the same period.
- Type: Outcome

Transplant patients' satisfaction
- Definition: level of overall satisfaction of transplant patients evaluated by means of a satisfaction survey.
- Formula: overall measurement of user satisfaction after scoring each item on the survey.
- Type: Outcome

TC: transplant centre.

Source: [32-46].

In the last decade, patient-reported outcome measures (PROMs) have been included as QIs in healthcare and they are increasingly recognised by regulators, clinicians and patients as valuable tools to collect patient-centred data [47]. PROMs are direct responses from patients without alteration or interpretation by a clinician. In addition, they may improve patient–provider communication, increase adherence and improve clinical outcomes. Perhaps the most crucial component of patient engagement is incorporating the lived patient experience in healthcare delivery [48].

PROMs have also been used in the field of transplantation and provide important information on the impact of a disease and/or its treatment from the patient perspective [46, 49]. Although transplant programmes may be hesitant to collect PROMs because of the need for additional resources, evidence suggests that incorporating these indicators into practice may lead to improved clinical outcomes (see Chapter 18) [48, 50].

17.6.5. Audits and quality evaluation

As in the donation process (see §17.5.3.1), the viability of a QI monitoring system should be evaluated by internal and external audits, thus enabling improvement measures to be subsequently taken as needed.

17.6.6. Documentation and registries, traceability, vigilance system, assessment and mitigation of risks,

complaints and recalls, and resource management

The entire process – starting from reception of the organ through to the transplantation and post-operative care – should be clearly documented, and criteria for each aspect should be defined. It is not exceptional to find that errors occurred because the documentation before transplantation was lacking. Clinicians should be made very attentive to documenting each step after receiving the transplant organ.

In order to detect possible inconsistencies in data collection, it is important to have a data-control system. Relevant data should be reviewed at transplant centre level, and at the allocation office, as a measure to automatically control the plausibility of data (e.g., laboratory values with normal creatinine and very high values for urea are not plausible).

The quality criteria relating to all of these support processes can be superimposed on those mentioned in the respective sections on quality management in organ donation, and so the reader is encouraged to review sections 17.5.3.2 to 17.5.3.8.

17.7. Final remarks

Although implementing a quality management system in the process of donation and organ transplantation may seem to be a complex process likely to involve an increased workload for the healthcare professionals concerned, the many advantages of doing so offset the initial effort. Some of these advantages include:

a. Task systematisation and standardisation of criteria in daily activities.
b. Support in visualising, analysing and improving workflow.
c. Involvement of personnel in daily activities, which contributes to better teamwork.
d. Definition, measurement and analysis of QIs, which makes results-based decision making easier.
e. Increased transparency and satisfaction of patients and healthcare professionals, and therefore improved trust in the transplant system (which in turn might be beneficial for organ donation).
f. Valuable management tool and increased motivation of healthcare personnel.
g. Promotion of continuous improvement.

Research agenda

From the literature and discussion of the available evidence, several topics have been identified for which evidence is inconsistent, insufficient or non-existent. The authors of this guide recommend that future research, where possible in well-designed randomised clinical trials, should focus on the following research gaps:

1 How to develop and implement a quality management system in organ donation and transplantation – at local, regional or national level – that includes quality improvement criteria, quality indicators and systematic internal and external donor auditing to monitor the level of quality of the service.
2 Identify best practices to ensure that all patients who are potential DBD and DCD donors are converted into actual donors.
3 Determine the best way to train healthcare professionals to proactively participate in donation programmes.
4 Develop standards that normal healthcare practice has to meet to be considered as good-quality in the donation and transplantation field.
5 Study the application of key performance indicators in donation and transplantation to determine the level of quality of the programme.
6 Examine the use of patient-reported outcome measures (PROMs) in the field of transplantation as a tool for improving clinical outcomes.
7 Develop value-based-care criteria for the evaluation of donation and transplantation programmes.

17.8. References

1. International Organization for Standardization, available at www.iso.org/iso/home/about.htm, accessed 22 July 2021.
2. Joint Commission on Accreditation of Healthcare Organizations, available at www.jointcommission.org/about_us/about_the_joint_commission_main.aspx, accessed 22 July 2021.
3. European Foundation for Quality Management, available at www.efqm.org, accessed 15 Feb 2020.
4. Cooperation for Transparency and Quality in Healthcare, available [in Dutch] at www.ktq.de/index.php, accessed 22 July 2021.
5. European Parliament. Directive 2010/53/EU of the European Parliament and of the Council of 7 July 2010 on standards of quality and safety of human organs intended for transplantation. *Official Journal of the European Union* 2010;53:14-29, available at https://eur-lex.europa.eu/legal-content/EN/ALL/?uri=celex%3A32010L0053, accessed 22 July 2021.
6. European Commission. Action Plan on Organ Donation and Transplantation (2009-2015): strengthened cooperation between member states. COM(2008)

819/3, available at http://ec.europa.eu/health/ph_threats/human_substance/oc_organs/docs/organs_action_en.pdf, accessed 23 July 2021.

7. Council of Europe. Recommendation Rec (2004) 19 of the Committee of Ministers to member states on criteria for the authorisation of organ transplantation facilities, 2004, available at https://wcd.coe.int/ViewDoc.jsp?id=802901, accessed 23 July 2021.
8. Council of Europe. Recommendation Rec (2001) 5 of the Committee of Ministers to member states on the management of organ transplant waiting lists and waiting times, 2001, available at https://wcd.coe.int/ViewDoc.jsp?id=190641, accessed 23 July 2021.
9. Council of Europe. Recommendation Rec (2006) 15 of the Committee of Ministers to member states on the background, functions and responsibilities of a National Transplant Organisation (NTO), 2006, available at https://wcd.coe.int/ViewDoc.jsp?id=1062653, accessed 23 July 2021.
10. European Parliament. Directive 2012/25/EU of 9 October 2012 laying down information procedures for the exchange, between member states, of human organs intended for transplantation. *Official Journal of the European Union* 2012;55:27-30, available at https://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2012:275:0027:0032:EN:PDF, accessed 23 July 2021.
11. Council of Europe. Recommendation Rec (2005) 11 of the Committee of Ministers to member states on the role and training of professionals responsible for organ donation (transplant 'donor co-ordinators'), available at https://wcd.coe.int/ViewDoc.jsp?id=870643, accessed 23 July 2021.
12. Council of Europe. Recommendation Rec (2006) 16 of the Committee of Ministers to member states on quality improvement programmes for organ donation, available at https://wcd.coe.int/ViewDoc.jsp?id=1062721, accessed 23 July 2021.
13. Coll E, Czerwinski J, De la Rosa G *et al.*, eds. *Guide of recommendations for quality assurance programmes in the deceased donation process.* DOPKI Project (European Commission), available at www.ont.es/publicaciones/Documents/Dopki%20GUIA.pdf, accessed 23 July 2021.
14. National Transplant Organisation (Spain). Good practice guidelines in the process of organ donation, 2011, available at www.ont.es/publicaciones/Documents/VERSI%C3%93N%20INGLESA%20MAQUETADA_2.pdf, accessed 23 July 2021.
15. Manyalich M, Guasch X, Gomez MP *et al.* and ODEQUS Consortium. Organ Donation European Quality System: ODEQUS project methodology. *Transplant Proc* 2013;45:3462-5.
16. Project ODEQUS (Organ Donation European Quality System). Criteria & quality indicators in organ donation, available at www.odequs.eu/pdf/ODEQUS_Quality_Criteria-Indicators.pdf, accessed 23 July 2021.
17. Martin-Loeches I, Sandiumenge A, Charpentier J *et al.* Management of donation after brain death (DBD) in the ICU: the potential donor is identified, what's next? *Intensive Care Med* 2019;45:322-30.
18. Squires JE, Coughlin M, Dorrance K *et al.* Criteria to identify a potential deceased organ donor. *Crit Care Med* 2018;46:1318-27.
19. Witjes M, Jansen NE, van der Hoeven JG, Abdo WF. Interventions aimed at healthcare professionals to increase the number of organ donors: a systematic review. *Crit Care* 2019;23:227, available at https://doi.org/10.1186/s13054-019-2509-3, accessed 23 July 2021.
20. Westphal GA, Robinson CC, Biasi A *et al.* DONORS (Donation Network to Optimise Organ Recovery Study): Study protocol to evaluate the implementation of an evidence-based checklist for brain-dead potential organ donor management in intensive care units, a cluster randomised trial. *BMJ Open* 2019 Jun 25;9(6):e028570. https://doi.org/10.1136/bmjopen-2018-028570.
21. Rubin HR, Pronovost P, Diette GB. From a process of care to a measure: the development and testing of a quality indicator. *Int J Qual Health Care* 2001;13:489-96.
22. Wight C, Cohen B, Roels L *et al.* Donor action: a quality assurance program for intensive care units that increases organ donation. *J Intensive Care Med* 2000;15:104-14.
23. Wesslau C, Grosse K, Krüger R *et al.* How large is the organ donor potential in Germany? Results of an analysis of data collected on deceased with primary and secondary brain damage in intensive care unit from 2002 to 2005. *Transpl Int* 2007;20:147-55.
24. Procaccio F, Rizzato L, Ricci A *et al.* Indicators of efficiency in potential organ donor identification: preliminary results from the national registry of deaths with acute cerebral lesions in Italian intensive care units. *Organs Tiss Cells* 2008;2:125-9.
25. De la Rosa G, Domínguez-Gil B, Matesanz R *et al.* Continuously evaluating performance in deceased donation: the Spanish quality assurance program. *Am J Transplant* 2012;12:2507-13.
26. Barber K, Falvey S, Hamilton C *et al.* Potential for organ donation in the United Kingdom: audit of intensive care records. *BMJ* 2006;332:1124-7.
27. ACCORD (EU Joint Action: achieving comprehensive coordination in organ donation throughout the European Union). Work Package 5: Increasing the collaboration between donor transplant co-ordinators and intensive care professionals, available at www.accord-ja.eu/sites/default/files/download_documents/accord_WP_5_ICU_%26_DTC_

Collaboration_FINAL_REPORT.pdf, accessed 23 July 2021.

28. European Centre for Disease Prevention and Control. Communicable disease threats report (CDTR), week 14, 1-7 April 2012: Contamination of a medical product – ViaSpan Multistate (worldwide), available at www.ecdc.europa.eu/sites/default/files/media/en/publications/Publications/120410-SUR-CDTR.pdf, accessed 23 July 2021.
29. Mathur AK, Talwalkar J. Quality measurement and improvement in liver transplantation, *J Hepatol* 2018; 68:1300-10. https://doi.org/10.1016/j.jhep.2018.02.034.
30. Morath C, Schemmer P, Zeier MG. Transplant quality programs. In: Kirk AD, Knechtle SJ, Larsen CP *et al.*, eds. *Textbook of organ transplantation*, 2 vols. New York: John Wiley & Sons, 2014, ISBN 1118889622, 9781118889626, pp. 1542-9.
31. Neuberger JM, Bechstein WO, Kuypers DRJ *et al.* Practical recommendations for long-term management of modifiable risks in kidney and liver transplant recipients. A guidance report and clinical checklist by the consensus on managing modifiable risk in transplantation (COMMIT) Group. *Transplantation* 2017; 101:S1–S56.
32. van der Veer SN, van Biesen W, Couchoud C *et al.* Measuring the quality of renal care: things to keep in mind when selecting and using quality indicators. *Nephrol Dial Transplant* 2014;29(8):1460-7. https://doi.org/10.1093/ndt/gft473.
33. Taber DJ, McGillicuddy JW, Bratton CF *et al.* The concept of a composite perioperative quality index in kidney transplantation. *J Am Coll Surg* 2014;218: 588-97.
34. Sultan H, Famure O, Phan NT *et al.* Performance measures for the evaluation of patients referred to the Toronto General Hospital's kidney transplant program. *Healthcare Management Forum* 2013;26:184-90.
35. Toussaint ND, McMahon LP, Dowling G *et al.* Implementation of renal key performance indicators: promoting improved clinical practice. *Nephrology (Carlton)* 2015;20(3):184-93. https://doi.org/10.1111/nep.12366.
36. Chakrabarti AK, Sheetz KH, Katariya NN *et al.* Do patient assessments of hospital quality correlate with kidney transplantation surgical outcomes? *Transplant Proc.* 2016;48:1986-92.
37. Patzer RE, Gander J, Sauls L *et al.* The RaDIANT community study protocol: community-based participatory research for reducing disparities in access to kidney transplantation. *BMC Nephrol* 2014 Oct 28;15: 171. https://doi.org/10.1186/1471-2369-15-171.
38. Sociedad Española de Trasplante Hepático. III Consensus Meeting of the Spanish Society of Liver Transplantation. Hepatitis C, living-donor liver transplantation, quality of liver grafts and of liver transplantation programs. *Cirugia Española (English edition)* 2011;89:487-504, available at www.elsevier.es/en-revista-cirugia-espanola-english-edition--436-pdf-S2173507711000160, accessed 23 July 2021.
39. Varona MA, Soriano A, Aguirre-Jaime A *et al.* Statistical quality control charts for liver transplant process indicators: evaluation of a single-center experience. *Transplant Proc* 2012;44:1517-22.
40. Therapondos G, Bohorquez H, Bruce DS *et al.* Liver transplantation at the Ochsner Clinic: quality and outcomes improvement. *Ochsner J* 2013;13(3):413-18.
41. Sclair SN, Carrasquillo O, Czul F *et al.* Quality of care provided by hepatologists to patients with cirrhosis at three parallel health systems. *Dig Dis Sci* 2016;61: 2857-67.
42. Muller X, Marcon F, Sapisochin G *et al.* Defining benchmarks in liver transplantation: a multicenter outcome analysis determining best achievable results. *Ann Surg* 2018;267:419-25. https://doi.org/10.1097/SLA.0000000000002477.
43. Bonow RO, Masoudi FA, Rumsfeld JS *et al.* ACC/AHA classification of care metrics: performance measures and quality metrics: a report of the American College of Cardiology/American Heart Association Task Force on Performance Measures. *J Am Coll Cardiol* 2008;52: 2113-17. https://doi.org/10.1016/j.jacc.2008.10.014.
44. Roussel MG, Gorham N, Wilson L *et al.* Improving recovery time following heart transplantation: the role of the multidisciplinary health care team. *J Multidiscip Healthc.* 2013;6:293-302.
45. Hullin R, Schmidhauser M, Regamey J *et al.* The impact of the multidisciplinary team approach on early mortality and acute cellular rejection after heart transplantation. *Eur J Heart Fail* 2016;18:233.
46. Brett KE, Ritchie LJ, Ertel E *et al.* Quality metrics in solid organ transplantation: a systematic review. *Transplantation* 2018;102:e308-30, https://doi.org/10.1097/TP.0000000000002149.
47. Mercieca-Bebber R, King MT, Calvert MJ *et al.* The importance of patient-reported outcomes in clinical trials and strategies for future optimization. *Patient Relat Outcome Meas* 2018;9:353-67. https://doi.org/10.2147/PROM.S156279.
48. Weldring T, Smith SMS. Patient-reported outcomes (PROs) and patient-reported outcome measures (PROMs). *Health Serv Insights* 2013;6:61-8. https://doi.org/10.4137/HSI.S11093.

49. Ju A, Chow BY, Ralph AF *et al.* Patient-reported outcome measures for life participation in kidney transplantation: a systematic review. *Am J Transplant* 2019 Aug;19(8):2306-17. https://doi.org/10.1111/ajt.15267.

50. Nelson EC, Eftimovska E, Lind C *et al.* Patient reported outcome measures in practice. *BMJ* 2015 Feb 10;350:g7818.

Chapter 18. Measuring outcomes in transplantation

18.1. Introduction

The aim of organ donation and transplantation is to try to provide all recipients on the waiting list with a chance to survive with an adequate quality of life. Therefore, organ transplantation should preferably occur just in time before end-stage organ failure becomes life-threatening or significantly impacts life expectancy and quality of life.

For donor relatives and/or the donors we are obliged to use any organ with the best chance of long-term function in the recipient selected. For organs and recipients with a limited functional and survival expectancy due to medical, biological (e.g., age) or transplantation factors, we have to find a balance in how we use such organs and transplant them into such recipients successfully. We have to weigh these factors and we have to make the best decision for both the recipient and the donor. We have to realise that sometimes it might be the best option not to choose the patient on the waiting list with the highest chance of dying or the longest waiting time, in order to avoid a futile transplantation.

This concept is probably best described with a 'benefit score' [1-2]. We are still dealing with a serious shortage of donor organs, so decisions are sometimes not in the best interest of a specific patient, but decisions should also consider the best interest of most patients in need of an organ. In order to monitor whether such decisions are correct or not, we have to ask ourselves whether all factors have been considered properly. Measuring and analysing outcomes will help to properly weigh all the factors involved, thereby enabling quality and safety control.

In organ transplantation we are dealing with a complex combination of donor, recipient and transplantation factors, including a large number of confounders that interact with each other in generating the outcome. Caution is also needed in the interpretation of data, because stakeholders and shareholders have various interests in the perception of results. Besides, the number of subjects investigated is usually limited and outcomes may be skewed.

The aim of this chapter is to provide some guidance on how to measure outcomes after transplantation in order to support the guidance in previous chapters on improving quality and safety, and how to best deal with the current shortage of organs with regard to allocation/organ offering.

18.2. End-points to measure, study period and confounders

As in any scientific study, end-points should be clearly defined. It should be explained what outcomes (e.g., patient or graft survival, death-censored or non-death-censored) are to be measured and whether short- or long-term results are evaluated [3]. Furthermore, it is important to describe the intention of the study and possible applications of the study results.

18.2.1. End-points to measure

Outcomes are usually measured by survival analysis. A survival analysis measures the time from the starting point of an observation, such as time of transplantation or entry onto waiting list, until occurrence of an event, such as graft failure or recipient death, and it is analysed for a certain study period. Another way of measuring outcome is by following up a recipient until a fixed time point when someone checks whether some event or measurement has been observed or not, e.g. patient- or graft survival, occurrence of acute rejection or return to work, or glomerular filtration rate (GFR) at one year after transplantation. Each method has its advantages and limitations.

Most commonly end-points are measured by survival analysis [4-7]:

a. Patient survival: time interval from transplantation to death of a recipient independently of graft-failure events. Therefore, the observation of patient survival should be extended beyond the end-point of graft-failure events or the record should state that observation has ended at this point.
b. Graft survival: time interval from transplantation to graft failure, regardless of whether graft failure or recipient death occurs first.
c. Graft survival death-censored: time interval from transplantation to graft failure, with the event of recipient death with a functioning graft censored, assuming that the recipient died with a functioning graft. This may be used to mitigate the issue of competing risks such as death with functioning graft *versus* graft failure caused by other issues. Then the assumption of proper graft function needs to be explained well because the event of death due to insufficient or poor graft function cannot be excluded.

Each end-point has its justification with pros and cons [5-6]. Best practice is to report all end-points or to clarify the use of only one particular end-point, such as graft survival, because multiple risk factors can cause graft failure in a set of combinations (e.g. death with a suboptimal functioning graft and recipient-related factors).

A second issue is the definition of graft failure, which should be clearly defined. For example, disregarding the event of re-transplantation, graft failure may be defined as:

a. in kidney transplantation: return to dialysis, or GFR below a threshold value;
b. in liver, heart and lung transplantation: return to waiting list due to malfunction, or actual date of retransplantation;
c. in pancreas transplantation: need for use of exogenous insulin (and how much) or Hb1Ac > 48 mmol/mol (> 6.5 %) according to the WHO diabetes definition.

It is obvious that, for such alternative failure events, the first occurrence of one of the alternative events should be imputed.

In kidney transplantation, either GFR or eGFR may be considered as the endpoint. Other surrogate markers can be discussed (e.g. albuminuria, donor specific anti-HLA antibodies), but they are not approved or validated yet. Other composite surrogate early endpoints have been proposed and investigated but not validated for clinical trials yet, e.g. iBox [8], total eGFR slope [9]. The interest in surrogate endpoints is that investigators want or need to predict outcome based on a representative marker as indicator to extrapolate a failure event occurring in the future, which can actually be assumed based on measured changes in that marker now.

18.2.2. Alternative outcome measures

Besides looking at survival as an outcome, it may be interesting to specifically look at other outcomes to better address where potential problems within the whole chain of transplantation exist and where potential improvements may have the highest impact. For example peri-operative complications are internationally scored by surgeons using the Clavien–Dindo classification [10]. For comparing differences between groups the Comprehensive Complication Index (an index based on the Clavien–Dindo classification) is probably even better suited [11].

Patient-Reported Outcome Measures (PROMs) can be included in studies as primary or secondary end-points and are increasingly recognised by regulators, clinicians and patients as valuable tools to collect patient-centred data [12]. PROMs could be defined as 'any report of the status of a patient's health condition that comes directly from the patient, without interpretation of the patient's response by a clinician or anyone else' (according to the U.S. Food and Drug Administration). PROMs may be a patient's report of:

a. disease symptoms or side effects,
b. functional outcome variables or
c. multidimensional constructs such as health-related quality of life (HR-QoL).

PROMs are often included as important clinical trial end-points and should be differentiated

from other types of patient-reported data, such as Patient-Reported Experience Measures (PREMs) or patient-reported behaviours, which may also be included as clinical trial end-points.

Most often, PROMs are assessed using questionnaires, often referred to as PROM measures. Validated PROM measures are used in clinical trials, as opposed to asking participants open-ended questions about their outcomes, to ensure that the questions, response options and general approach to assessment are standardised for all participants.

PROMs provide important information on the impact of a disease and/or its treatment from the patient perspective. Therefore, PROMs should be included in studies as well as clinical practice to ensure that the impact of a disease or treatment is adequately assessed. Ongoing methodological research is important for determining what constitutes best practice when applying PROMs in medical research (see §17.6.4).

18.2.3. Study period

Occurrence of a particular complication can also be analysed in relation to the time interval from transplantation until manifestation of the complication, which might be acute rejection or diagnosis of ischaemia-type biliary lesion (ITBL) in liver transplantation. There should also be consideration of the issue of competing risks, as in death of the recipient for other reasons or re-transplantation for other reasons.

This is a key problem: what to do with subjects in a study who cannot be observed for the occurrence of an event because they have dropped out of the study due to competing failure events or have been lost to follow-up for unknown reasons. In such a case the subject has no chance to experience the event of interest. One example of how to handle this problem would be a decision to censor deaths during the observation period when conducting survival analysis that focuses on graft failure. Equally problematic are fixed measurements at certain time points, such as numbers returning to work within one year after transplantation, if some recipients have died postoperatively with a non-transplant-related issue.

It should also be clearly indicated whether outcome is measured on the basis of intention to treat or on the basis of an actually occurring intervention. In both cases it should be mentioned what was or is done with the cases not receiving the intervention or the cases where there was deviation from the intention to treat.

18.2.4. Confounders

The examples in section 18.2.2 show that looking exclusively at one risk factor will not give a correct view without adjustment for confounders. On the other hand, failure events or complications may be caused by one common bundle of risk factors; for example, graft failure and/or ITBL may be caused as a result of prolonged ischaemia times, incorrect flush of organ and bile ducts at procurement, prolonged anastomosis time or arteriosclerosis. This requires careful analysis of all the individual factors and their contribution to the global result.

For survival analysis, the following methods are often used:

a. Kaplan–Meier analysis, which shows up the influence of a single risk factor on the time interval after transplantation until the failure event occurs, without adjustment for confounders. The risk factor can be dichotomous or a group of classes, or it may be a continuous variable split into certain categories. With 'increasing risk' of the risk factor, a monotonously increasing sequence of curves should be visible without any criss-crossing of the curves. Furthermore, the number of cases at risk diminishes with time and therefore care should be taken in deriving strong conclusions if 'the numbers at risk' are too low.

b. In Cox regression models, multiple variables can be considered for their combined influence on outcome. This may be stated as adjustment for confounders. The risk of a specific risk factor is described by the Hazard ratio: the risk is significantly increased when the Hazard ratio and the 95 % confidence interval are above 1, and there is protection from risk when both are below 1. When the 95 % confidence interval crosses 1, there is no significant change in risk. Still no adjustment exists for confounders not considered in the model. Therefore, selection of variables in the statistical model is crucial and should be explained properly. For continuous variables in the model, the Hazard ratio should be explained as related to increment in one unit or increment over the whole population. In such multivariable models, conclusions about a single factor require careful consideration of the confounders analysed too. For proper analysis of competing risk events the sub-distribution hazards according to the method of Fine and Gray can be used – especially for long-term analysis. Otherwise the same principles apply as have been mentioned for Cox regression [13-18].

It is recommended that outcome studies are planned and results are discussed with an expert in medical statistics because valid and reliable data require careful study planning, and pitfalls exist in the interpretation of data in survival analysis. For details, please refer to the specific literature (e.g. further statistical test used). Some examples of survival analysis are shown in Table 18.1. Further, good

Table 18.1. **Some examples of organ-specific outcome measurements**

Indicator	Heart	Lung	Liver	Kidney	Pancreas	Intestine
Patient survival	**Time interval: death; Clarify cause of death**					
Graft survival (uncensored for death of recipient)	Time interval until death with functioning graft or re-transplantation or return to assist device or graft-ectomy, whichever occurs first.	Time interval until death with functioning graft or re-transplantation or graft-ectomy or return to ECMO, whichever occurs first.	Time interval between transplant and graft loss secondary to either re-transplantation or recipient death, whichever occurs first.	Time interval until return to dialysis or death, whichever occurs first. Alternatively time interval to return to dialysis can be determined by a cut-off value of the glomerular filtration rate (GFR).	Time interval until return to exogenous insulin use (e.g. ≥ 0.5 IU/kg/day for > 90 consecutive days) or HbA1c > 48 mmol/mol (6.5 %) (diabetes according to WHO) or recipient death, whichever occurs first.	Time interval until death with functioning graft or re-transplantation or failure (e.g. re-introduction of enteral nutrition) or graft-ectomy, whichever occurs first.
	Currently several definitions are used, so this parameter requires clarification, including the cause of failure.					
Graft survival (censored for death of recipient)	As above but censored for death of recipient with functioning graft as a no-failure event. This is a very critical issue, because authors must meticulously state the exact definitions, being used in the article, of when they consider a graft as still functioning or not functioning. In cases of marginal or impaired organ function, the interaction of recipient death and poor graft function cannot be ruled out.					
Graft-related complications	It is arguable whether occurrence of particular complications may be used as an outcome measurement or not, and also how the time interval between transplantation and event is considered. This must be defined in the study protocol.					
	e.g. coronary heart disease	e.g. bronchiolitis obliterans	e.g. biliary leakage; ITBL	e.g. proteinuria	e.g. pancreatitis, thrombosis	
Functional parameter	e.g. cardiac output	e.g. gas exchange	e.g. coagulation, liver enzymes	e.g. GFR	e.g. HbA1c, amount of insulin used	
Delayed graft function (DGF)	Usually defined as a yes/no event based on items listed below and as outlined in the study protocol					
	e.g. until weaned off inotropics or assist device	e.g. until weaned off ventilator or ECMO	In liver transplants, it is referred to as slow or intermediate graft function (SGF or IGF). In that case, cut-off levels need to be stated in the manuscript.	Despite multiple definitions of DGF in kidney transplants, 69 % of studies use this definition: DGF is the need for dialysis within the first week after transplantation [10]	e.g. until weaned off insulin	
Primary non-function of graft (PNF)	e.g. never weaned off inotropics or assist device	e.g. never weaned off ventilator and/or ECMO	e.g. re-transplantation or death without initial function	e.g. never weaned off dialysis	e.g. never weaned off insulin	
Reperfusion damage						
Duration of stay at ICU	Time interval					
Duration of hospital stay	Time interval					
Quality of life	Parameters to be extracted from rehabilitation medicine					

ECMO = extracorporeal membrane oxygenation.

Time interval: can be either two measurements as fixed time points (start time, end time) or a single measurement of duration of transplantation or elapsed time until specific event occurs. This list is not exhaustive, and the factors mentioned can be combined with each other. In the literature, multiple definitions are used for graft function or failure that might be justified in the context of that specific published study.

examples of quality indicators are provided in §17.6.4 and Figure 17.1. These examples are ready-to-use indicators, which need careful consideration of the issues outlined in this chapter before final conclusions can be drawn.

In outcome analysis, static end-points need exact definitions, which need to be unambiguously specified in the study protocol. These end-points can be categorical measurements or metric measurements associated with a time point. Also the defined parameters must include the time that is to elapse before checking whether this event has occurred or not (see Table 18.1 describing examples of organ-specific end-points). Absolute numbers of cases and their percentages are of interest in dichotomous factors as well as in the distribution of continuous variables. It is helpful to adjust single parameters for confounders by appropriate regression models. Again, it is recommended that results are discussed with an expert in medical statistics as pitfalls exist in study design and interpretation of data.

18.3. Selection of and adjustment for covariates or treatment bias

Care is required when selecting variables to be included in an outcome analysis study [5-6, 19]. Enough data exist to show that outcome depends on donor quality and the recipient's medical condition, but also on the expertise of a centre and other transplantation factors such as organ preservation and donor management. Overlooking important confounders will result in incorrect analysis. Without proper consideration of this risk, the study will fail to yield reliable data and the results might become questionable.

Depending on the case-mix of the population investigated, different results may be expected: naturally, centres specialising in paediatric transplantation will have different data from centres specialising in adult transplantation, and units transplanting organs from extended-criteria donors will have outcomes that probably are different to those achieved in units not utilising this donor source. Proper correction for case-mix will be required. The use of propensity scores is currently advocated as a method to compensate for the bias caused by confounders not expected (e.g., overlay due to effects of immunesuppressive treatment in a study). However, adequate identification of possible confounders and correction for risk factors is essential before methods such as propensity scores are used.

Therefore it is important to adjust for covariates by multivariable methods before a result of single variable analysis can be confirmed [5-6, 19]. The study report should include all details about risk factors considered but also risk-factors that have or have not been considered, due to lack of data or sample size, for example. When an association exists between multiple risk factors, which all have an impact on outcome, then using a single risk factor – that subsequently depends on the other factors – has to be done with caution [20].

When defining end-points for measuring outcomes and selecting risk factors that potentially influence these outcomes, it has to be kept in mind that all relevant clinical factors are to be included in the statistical model [5-6]. A transparent explanation of this process is mandatory. Best practice is to perform external validation of the thesis in an independent study group [18]. It is recommended that validation of such risk factors is repeated over time, because their influence might be due to chance or they might even become outdated in their prognostic contribution (e.g., the risk factor of donor hepatitis C viraemia will change in its relevance due to possible treatment by direct-acting antiviral agents in the recipient).

Two reviews – about quality metrics in solid organ transplantation and variables to be collected in transplantation for improving risk prediction – have summarised which risk factors should be considered to predict outcome and what is their expected impact. In this context always arises the issue of how to handle missing data and how to report this problem properly [23].

When outcome-prediction models are to be imported from one healthcare system into another, it is essential that the validation process is repeated with a representative study population within such a healthcare system. However, discrimination and calibration of the prognostic system might then fail and the whole process of developing a prognostic scoring system would have to be repeated. Two important limitations exist. For investigation of a particular risk factor in many populations, there may be an insufficient number of cases and/or events observed and therefore no conclusions with proper risk adjustment are possible. Furthermore, for most study groups in the range of the extreme values of risk factors, a predictive model performs well, whereas in the majority of the cases within the range of intermediate values of the risk factor no acceptable degree of discrimination exists (e.g., Donor Risk Index for kidneys [24]). These issues have to be explained well.

18.3.1. Long-term follow-up *versus* short-term follow-up

Ideally, we would have decades of data from monitoring the long-term function of grafts, using patient-, graft- and death-censored measures of graft survival as well as quality-of-life measurement of the recipient over the timeline of survival. Manifestation of complications due to existing risk factors or avoidance of complications by interventions could be monitored precisely in their short-term and long-term effects.

Unfortunately we cannot wait decades to adapt interventions and decisions while withholding optimised organ-replacement therapy for future recipients. Therefore science has to look for surrogate markers to predict long-term function by short-term observations and extrapolation of the assumed risk into the future, for example by patient-, graft- and death-censored graft survival as well as quality-of-life measurement of the recipient, limited to short periods of one, two, three or five years. In a second step, studies should confirm the primary assumptions by long-term follow-up.

Most complications occur during the early period after transplantation (typically the first two years) but, after this first and steep incline of risk, complication rates plateau to a more constant level over time. However, some risk factors have a higher impact during the early post-transplant period (e.g., infection during the early phase of intensive immunosuppression or pancreatic graft thrombosis [25]) whereas others become more important in the longer term (e.g., death due to cancer after many years of immunosuppression). This requires adjustment in the methods of measuring outcome. It is evident that early complications could be well described with only a short follow-up period, whereas long-term complications and outcomes would be missed in such a study.

The issue of time-dependent covariates and competing risks should be considered too. For example, when monitoring outcomes for patients put on the waiting list, then it would be of interest to know what happens in candidates not being given a transplant *versus* candidates with transplants after having survived a certain waiting time and being exposed to the event of graft failure [26]. Data-driven analytics-based models may assist in the complex decision of whether to accept or forgo a current offer in anticipation of a future higher-quality offer [27].

18.3.2. Surrogate markers for long-term function

Surrogate markers for long-term survival or assumed indicators for reliable prognosis in long-term survival should be described in the researcher's consideration of their assumptions. The proof of concept should be provided by long-term measurement of hard end-points (e.g., by survival analysis or description of quality of life achieved). For example, enough data exist for the surrogate marker GFR measured and prognosis after kidney transplantation regarding graft survival. On the other hand, several studies have shown that kidney grafts from donors with acute kidney injury can be used without impact on outcome, while they also report the need for post-operative dialysis requirements. Clearly, delayed graft function (DGF) cannot be used as a surrogate marker in such studies because all patients would fall within the definition for DGF. This needs careful explanation of what is being investigated.

18.3.3. Centre effect and duration of study period

Adjustment for centre effect and length of study period should be considered too [29-30]. Depending on the case-mix of the donor and recipient populations investigated, different results are observed. This must be considered, when communicating the indicators as suggested in section 17.6.

There are various means of analysing or presenting centre-specific outcome measures and correcting for different risk profiles per centre. These risk profiles depend heavily on access to suitable donor organs and the number of patients on the waiting list in the particular centre analysed. For example, centre outcome could be analysed by comparing only 'benchmark' cases, that is, reference donor organs transplanted into referent recipients [31]. However, due to current organ scarcity most transplantations are being performed using extended-criteria donor organs in higher-risk recipients and benchmark cases include only about 25 % of all transplantations performed, varying widely between centres (8-49 %). Another option is to correct for 'case-mix' by correcting for higher-risk donor and recipient parameters [32].

For a study with a long period of recruiting cases, a bias for changes in medicine should be considered. This can be corrected by noting specific study periods in relation to known milestones in medicine or, if they are not applicable, by including a continuous variable of study time.

In a small series there is a risk of bias caused

by the interest of the study and recruiting of subjects. Pilot studies are under pressure to push patients through the study period in order to obtain results. This issue requires confirmation by monitoring the usability of study data in clinical practice by independent control studies and proper follow-up of the initial study population.

In the case of an analysis of a single centre, all adjustments for confounders or involved risk factors should be applied in order to eliminate the issue of a policy of avoiding risk behaviour due to external control with open access. Since we have an organ shortage, single centres should not be punished for using higher-risk organs when they are able to achieve results equivalent to other centres. However, transparency should be promoted and therefore it is essential to show or publish results. Of course, results should be shown in the context of donor quality and recipient condition, and adequate correction for involved risks (case-mix) is essential. This does not exclude careful monitoring of a trend analysis towards failure accumulation in a single institution caused by other issues.

Furthermore, due to different policies in healthcare systems, centre effects may not be attributable to donor-, recipient- or procedure-related risk factors but to other issues based on the concept of that particular healthcare system [33].

18.3.4. Pressure to publish

Most studies are under pressure to publish quickly. Exhaustive waiting for long-term results might not be in the interest of stakeholders or shareholders. Furthermore, study results might be misinterpreted to better match the interests of the readers; negative results are often less attractive to the publisher but might sometimes be equally important.

18.4. Challenge of statistics

For readers of studies who are not familiar with all details of statistics, the interpretation of data and conclusions is difficult. Authors should consider this. When talking about models, authors should always state clearly how good the prognostic values are and what limitations exist.

Regarding the quality of predictive models, c-statistics might be helpful: according to Harrell, a c-value of 0.5 corresponds to a random experiment of flipping a coin, while values of > 0.7 are acceptable as predictions and values of > 0.9 can be regarded as perfect predictions. In the transplantation setting it will be difficult to achieve a c-index of > 0.7 because we want to predict outcomes for people who have received an organ transplant, a procedure that is always influenced by many uncontrollable factors and events, with low numbers of cases. (Note that c-values are time- and outcome-dependent [35].) This uncontrollable aspect should be well considered, especially when such models are used to discard or to use donor organs without further individual risk–benefit assessment of the donor–recipient combination.

18.4.1. Profiles of risk factors change over time

Established models used in discussion of risk factors have to be re-evaluated regularly for their validity because donor populations and recipient populations change in their case-mix over time (e.g., donor age, cause of death, co-morbidities, recipient age, human leukocyte antigen immunisation, therapy concepts, new and more effective immune-suppressive drugs or other technologies). Risk factors themselves may change, or new risk factors may become apparent. New procedures (e.g., machine perfusion, normothermic regional reperfusion, minimally invasive procedures) may improve outcome and may subsequently change donor-risk evaluation. Therefore it is necessary to continually re-examine the models and concepts in use in order to identify changes and re-educate users with the aim of changing attitudes to risk–benefit assessment to ensure that it is properly performed.

18.4.2. Monitoring of trends in performance

Although we are faced with limited resources financially as well as in the number of organs, we have to ensure that an appropriate and optimal quality is achieved for each transplantation [5, 36]. Centres and/or regions that, after correction for risk factors based on the case-mix of recipients and donor grafts, show a performance above average should be monitored to help other centres in copying best practice. At the same time, outliers below average should be evaluated for identification of known or possible new risk factors explaining the inferior outcomes. It is important to keep in mind that unavoidable differences may exist between various centres, regions and countries [33].

Within centres and healthcare systems a trend in outcome data should be monitored too in order to identify changes in risk factors at an early stage [37]. When monitoring such data it is important to identify whether, either at single institutions or in the healthcare system as a whole, there is any inappropriate risk-avoiding behaviour when selecting

transplant recipients and grafts with the sole purpose of positively influencing outcome measures. Note that the monitoring of outcomes of transplantation should include the whole process, starting with entry of patients onto the waiting list and their exposure to transplant-associated risks later on [26, 29-30]. Transplantation outcomes well below average may be explained by risk avoidance or risk acceptance in the choice of recipients or grafts.

Different methods have been applied to monitor such trends, each method having its own strengths and weaknesses. Despite careful interpretation of the data, a low number of cases per transplantation unit might be a limiting factor for the application of regression models. In order to have an appropriate set of primary data in registries, all resources of electronic data availability should be used (e.g., waiting list database, donor database, allocation database) so that double documentation of existing data is avoided and clinically relevant data can be added to the registry. Personal data protection should be assured when analysing registry data.

For research purposes, secondary data analysis might help to monitor for trends in the whole healthcare system. For a primary approach, some quality indicators exist and are in use, with and without adjustment for risk factors (see §17.6 and published national data).

18.5. European transplant registries

Different transplantation registries exist in Europe within the Council of Europe member states as well as internationally. In the European Union the EDITH project is proposing a European kidney transplant registry [38]. Within this project a dataset useful for studies will be provided. This translates into the conclusion that we need an agreement on which data should be collected prospectively in donation and transplantation studies for analysis quality. From the point of view of this guide, this project should be expanded to all organs in order to assure quality and safety as well as transparency in organ transplantation. Previous chapters have provided guidance on how to manage the donation and transplantation process. Thereby the standardised data used for cross-border organ exchange may be considered as one set of data to be used.

18.6. Conclusion

Measuring outcome after transplantation is complex. No perfect method exists to give the user a complete picture. Instead, each approach has its limitations and merits. If a combination of methods produces an easy-to-understand result, then the outcome reported should be interpreted with caution and will sometimes need further investigation, whether it is a desirable or undesirable result.

Especially when performing analysis for quality assurance of centre-specific performance, all efforts must be undertaken to educate all staff about what is inappropriate risk-avoiding behaviour, so that medical professionals and non-medical people do not try to avoid all risk. On the other hand, it cannot be accepted that a poorly performing institution can hide behind multiple excuses (e.g., data protection, burden of data collection for quality assessment). Therefore, central data collection, transparency, analysis and quality assessment are essential in any organisation to monitor and further improve outcomes after transplantation [38]. The key message of the SONG project (Standardised Outcomes in Nephrology) is 'Clinical trials that report important and relevant outcomes can help patients and their clinicians make decisions about treatment' [39]. Therefore, it is helpful to perform studies of outcomes with appropriate transparency as well as reproducible methods and standards.

Research agenda

From the literature and discussion of the available evidence, several topics have been identified for which evidence is inconsistent, insufficient or non-existent. The authors of this guide recommend that future research, where possible in well-designed randomised clinical trials, should focus on the following research gaps:

1 Effectiveness of collaboration by European registries in providing data for confirmation of the content in chapters 6 to 13 of this Guide.
2 Exclude bias related to national healthcare systems.
3 Are the methods and end-points suggested in Table 18.1 really helpful, or are they based on unconfirmed assumptions?
4 Do alternative end-points exist that would allow prediction of long-term outcome on the basis of short observation periods?

18.7. References

1. Merion RM, Schaubel DE, Dykstra DM *et al.* The survival benefit of liver transplantation. *Am J Transplant* 2005;5:307-13.
2. Bae S, Massie AB, Thomas AG *et al.* Who can tolerate a marginal kidney? Predicting survival after deceased donor kidney transplant by donor-recipient combination. *Am J Transplant* 2019;19:425-33.
3. Blok JJ, Putter H, Metselaar HJ *et al.* Identification

and validation of the predictive capacity of risk factors and models in liver transplantation over time. *Transplant Direct* 2018;4:e382. https://doi.org/10.1097/TXD.0000000000000822.

4. European Framework for the Evaluation of Organ Transplants (EFRETOS). Report on the use of the European Registry of Registries (EFRETOS). Leiden, Netherlands: Eurotransplant Foundation, 2011, available at https://webgate.ec.europa.eu/chafea_pdb/assets/files/pdb/20081101/20081101_d09-00_oth_en_ps.pdf, last accessed 26 July 2021.
5. Neuberger J, Madden S, Collett D. Review of methods for measuring and comparing center performance after organ transplantation. *Liver Transpl* 2010;16:1119-28.
6. Snyder J, Salkowski N, Kim J *et al.* Developing statistical models to assess transplant outcomes using national registries. The process in the United States. *Transplantation* 2016;100:288-94.
7. Singh S, Kaplan B, Kim J. Multivariable models in clinical transplant research: principles and pitfalls. *Transplantation* 2015;99:2451-7.
8. Holtkamp F, Gudmunsdottir H, Maciulaitis R *et al.* Change in albuminuria and estimated GFR as end points for clinical trials in early stages of CKD: a perspective from European regulators. *Am J Kidney Dis* 2020;75:6-8. https://doi.org/10.1053/j.ajkd.2019.07.019.
9. Loupy A, Aubert O, Orandi B *et al.* Prediction system for risk of allograft loss in patients receiving kidney transplants: international derivation and validation study. *BMJ* 2019;366:l4923. https://doi.org/10.1136/bmj.l4923.
10. Dindo D, Demartines N, Clavien PA. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. *Ann Surg* 2004;240:205-13.
11. Slankamenac K, Nederlof N, Pessaux P *et al.* The comprehensive complication index: a novel and more sensitive endpoint for assessing outcome and reducing sample size in randomized controlled trials. *Ann Surg* 2014;260:757-62; discussion 762-3. https://doi.org/10.1097/SLA.0000000000000948.
12. Mercieca-Bebber R, King M, Clavert M *et al.* The importance of patient-reported outcomes in clinical trials and strategies for future optimization. *Patient Relat Outcome Meas* 2018;9:353-67.
13. Scrucca L, Santucci A, Aversa F. Competing risk analysis using R: an easy guide for clinicians. *Bone Marrow Transplant* 2007;40:381-7.
14. Scrucca L, Santucci A, Aversa F. Regression modelling of competing risk using R: an in depth guide for clinicians. *Bone Marrow Transplant* 2010;45(9):1388-95.
15. Fine JP, Gray RJ. A proportional hazards model for the subdistribution of a competing risk. *J Am Stat Assoc* 1999;94:496-509.
16. Hoffmann W, Latza U, Baumeister S *et al.* Guidelines and recommendations for ensuring Good Epidemiological Practice (GEP): a guideline developed by the German Society for Epidemiology. *Eur J Epidemiol* 2019;34:301-17. https://doi.org/10.1007/s10654-019-00500-x.
17. Fonseca I, Teixeira L, Malheiro J *et al.* The effect of delayed graft function on graft and patient survival in kidney transplantation: an approach using competing event analysis. *Transpl Int* 2015 Jun;28(6):738-50. https://doi.org/10.1111/tri.12543.
18. Royston P, Altman DG. External validation of a Cox prognostic model: principles and methods. *BMC Med Res Methodol* 2013;13:33. https://doi.org/10.1186/1471-2288-13-33.
19. Heinze G, Dunkler D. Five myths about variable selection. *Transpl Int* 2017;30:6-10.
20. Debout A, Foucher Y, Trébern-Launay K *et al.* Each additional hour of cold ischemia time significantly increases the risk of graft failure and mortality following renal transplantation. *Kidney Int* 2015;87:343-9.
21. Brett K, Ritchie L, Ertel E *et al.* Quality metrics in solid organ transplantation: a systematic review. *Transplantation* 2018;102:e308-30.
22. Almasri J, Tello M, Benkhadra R *et al.* A systematic review for variables to be collected in a transplant database for improving risk prediction. *Transplantation* 2019;103:2591-2601.
23. Budhiraja P, Kalplan B, Mustafa R. Handling of missing data. *Transplantation* 2020;104(1):24-6. https://doi.org/10.1097/TP.0000000000002865.
24. Rao PS, Schaubel DE, Guidinger MK *et al.* A comprehensive risk quantification score for deceased donor kidneys: the kidney donor risk index. *Transplantation* 2009;88:231-6.
25. Finger EB, Radosevich DM, Dunn TB *et al.* A composite risk model for predicting technical failure in pancreas transplantation. *Am J Transplant* 2013;13:1840-9.
26. Schold J, Buccini L, Goldfarb D *et al.* Association between kidney transplant center performance and the survival benefit of transplantation versus dialysis. *Clin J Am Soc Nephrol* 2014;9:1773-80.
27. Bertsimas D, Kung J, Trichakis N *et al.* Accept or decline? an analytics-based decision tool for kidney offer evaluation. *Transplantation* 2017;101:2898-2904.
28. Neuberger J, Bechstein W, Kuypers D *et al.* Practical recommendations for long-term management of modifiable risks in kidney and liver transplantation recipients: a guidance report and clinical checklist by the consensus on managing modifiable risk in

transplantation (COMMIT) group. *Transplantation* 2017;101(Suppl): S1-S56.

29. Massie AB, Segev DL. The rate of false flagging due to statistical artifact in CMS evaluations of transplant programs: results of a stochastic simulation. *Am J Transplant* 2013;13:2044-51.
30. Salkowski N, Snyder JJ, Zaun DA *et al.* Bayesian methods for assessing transplant program performance. *Am J Transplant* 2014;14:1271-6.
31. Muller X, Marcon F, Sapisochin G *et al.* Defining benchmarks in liver transplantation: a multicenter outcome analysis determining best achievable results. *Ann Surg* 2018;267:419-25. https://doi.org/10.1097/SLA.0000000000002477.
32. Blok JJ, de Boer JD, Putter H *et al.* The center effect in liver transplantation in the Eurotransplant region: a retrospective database analysis. *Transpl Int* 2018;31: 610-19. https://doi.org/10.1111/tri.13129. Epub 2018 Mar 5.
33. Gondos A, Döhler B, Brenner H, Opelz G. Kidney graft survival in Europe and the United States: strikingly different long term outcomes. *Transplantation* 2013;95:267-74.
34. Siedlecki A, Irish W, Brenan DC. Delayed graft function in the kidney transplant. *Am J Transplant* 2011;11;2279-96.
35. de Boer JD, Putter H, Blok JJ *et al.* Predictive capacity of risk models in liver transplantation. *Transplant Direct* 2019;5:e457. https://doi.org/10.1097/TXD.0000000000000896.
36. Oniscu G, Ravanan R, Wu D *et al.* Access to transplantation and transplant outcome measure (ATTOM): study protocol of a UK wide in-depth, prospective cohort analysis. *BMJ Open* 2016;6:e010377. https://doi.org/10.1136/bmj-open-2015-010377.
37. Salkowski N, Gustafson S, Wey A, Snyder J. KDPI obscures trends in absolute donor risks [abstract]. *Am J Transplant* 2017;17:Suppl 3, available at https://atcmeetingabstracts.com/abstract/kdpi-obscures-trends-in-absolute-donor-risk/, accessed 26 January 2022.
38. European Union: Edith project, available at https://edith-project.eu/, last accessed 26 July 2021.
39. SONG Initiative [Standardised Outcomes in Nephrology]. *The SONG Handbook*. Version 1.0 June 2017, Sydney, Australia. Available at https://songinitiative.org/reports-and-publications/, last accessed 26 July 2021.

Chapter 19. Communication of risk and shared decision-making

19.1. Introduction

Patient safety and transparency regarding the risks and benefits of transplantation are critical elements across the entire process of transplantation. Both safety and transparency are essential to build and maintain trust between transplant physicians, patients and (where appropriate) living donors (LD), and to preserve public trust in transplantation. Advances in surgical techniques, immunosuppressive medication, assessments of donor-related risks, and peri-operative and post-operative management of LDs and transplant recipients have made organ transplantation a safe and effective treatment for end-stage organ disease or failure. Nevertheless, transplantation is not without risk. As discussed earlier in this Guide, risks can be associated with the surgical procedure, lifelong immunosuppressive regimens and transmission of infectious diseases (see Chapter 8), malignancies (see Chapter 9) or other diseases (see Chapter 10). Likewise, LD transplantation carries potential risks in peri-operative and post-operative phases for LDs and, as for deceased donor transplantation, risks of disease transmission to transplant recipients (see Chapter 13). It is one of the fundamental duties of all involved experts to minimise these risks.

The duty to communicate the risks and benefits of transplantation to transplant recipients and LDs is a legal and ethical requirement, unless the patient explicitly requests and undersigns non-disclosure of certain risks. From a legal perspective, physicians are expected to disclose any information and any risks that the patient might consider important for them in order to make an informed decision, whereas, from an ethical perspective, informed consent fulfils the principle of patient autonomy. However, the outlook that patients and physicians have on risks and benefits and on which information is necessary to make an informed decision can be diverging. The process of informed consent is inherently a tension between the principles of beneficence/non-maleficence ('do no harm') and patient autonomy. This means that the clinical perspective, including clinical indications based on well-established protocols, does not necessarily match patients' preferences and individual, subjective considerations or specific life circumstances. The term 'communication' derives from the Latin word *communis*, which means 'common' [1]. Therefore, 'to communicate' (Latin *commūnicāre*) is inherently related to the concept of sharing and putting in common. 'Communication', within this context, can thus be used interchangeably with 'interaction', highlighting the intrinsically relational nature of consent, which must not be intended as a merely informative process.

Additionally, whenever serious adverse reactions and/or events (SAREs) occur – such as disease transmission as a result of transplantation or the death of an LD, and others, such as renal failure – a co-ordinated, timely and thoroughly planned communication strategy with all relevant stakeholders is critical to preserve public trust and to minimise the

potential for indirect negative effects on people's willingness to donate.

The purpose of this chapter is twofold. First, it aims to provide some guidance regarding the communication of risk to transplant candidates, recipients and LDs in a variety of settings, with a focus on the process of informed consent. Second, it seeks to deliver indications on the need for strategies to be adopted for appropriate communication with stakeholders following the occurrence of SAREs in the practice of organ donation or transplantation. In the process, it identifies existing gaps so as to inform the agenda for future research.

19.2. Communication of risk and consent for solid organ transplantation

Communication of risk requires consideration of multiple donor, recipient and transplant-related factors which may vary case by case. Although tools and protocols exist for donor and recipient clinical assessments, each patient must be treated individually. This is critical to evaluation of the risk–benefit ratio for individual recipients and LDs and, equally, to ascertain that the patient's or LD's perspective has been incorporated in the decision-making process leading to organ transplantation or living donation. Life goals, needs, values and preferences will be unique to individual transplant candidates, recipients and LDs, and may diverge from what physicians consider to be the best clinical solution.

Organ transplantation is a lifelong process, and proper communication should be in place early in the course of pre-transplant evaluation and across the entire continuum of care, so as to foster trust and enable shared decision making (SDM). Enforcing a lifetime relationship is critical because risks can emerge in the follow-up, with the potential to compromise successful outcomes of transplantation and living donation. SDM is broadly recognised as the most desirable and ethical model of the patient–physician relationship, moving away from earlier paternalistic models of care [2]. SDM is defined as "an approach where clinicians and patients share the best available evidence when faced with the task of making decisions, and where patients are supported to consider options, to achieve informed preferences" [3]. SDM includes two core elements: communication of risk and clarification of patient values. The former occurs when healthcare professionals communicate the benefits and harms of a medical treatment based on the best scientific evidence at a given time. Clarification of values entails elucidating what is most important to patients and their families [4].

Therefore, it follows that consent is more than just a signature on a piece of paper. Rather, as stated in the Report of the International Bioethics Committee of UNESCO, it is a relational process "where discussion with the patient is needed at several succeeding points in time, through an ongoing dialogue" [5]. Regarding this aspect, Brenner and colleagues have pointed out that the informed consent form is not a substitute for patient education; rather, it serves to provide evidence that discussions have occurred [6]. Therefore:

a. informed consent forms should be understandable, and the process should be intended as a means to educate the patient – and to ensure that comprehension has been achieved – rather than a tool to prevent lawsuits;
b. the physician/surgeon should abstain from paternalistic approaches in dealing with uncertainty and should rather turn uncertainty into an opportunity to build a therapeutic alliance with the patient;
c. proper patient education does not entail providing the patient with a comprehensive list of all the potential complications of medical treatment. In contrast, a well-informed patient should be one who actively participates in a dialogue about the risks that are most relevant to the individual decision-making process;
d. a concise, comprehensible note in the patient's medical record notifying that discussions have occurred with the patient and (or) the patient's family may be more effective than a signed but lengthy and difficult-to-read form.

When faced with high-risk procedures, entailing low levels of certainty, and in the presence of two or more treatment alternatives, the processes of informed consent and SDM overlap [7]. Some research suggests that SDM has the potential to positively affect multiple patient outcomes. It is frequently associated with affective-cognitive outcomes (understanding, satisfaction, trust), but less often with behavioural (adherence, treatment decisions, health behaviours) and health outcomes (symptom reduction, quality of life, physiological measures) [8]. Other studies reveal that SDM interventions incorporating multiple sessions may improve patients' affective (e.g. satisfaction), behavioural (e.g. adherence) and health outcomes (e.g. depression and well-being), especially when making longer-term decisions and in chronic disease settings. Also, in patients with chronic illnesses, the active involvement of patients

through SDM increases the likelihood of adherence to health behaviours, and engagement in health-promoting or health-maintaining behaviours [9, 10]. In the organ transplantation setting, SDM serves the function of integrating the clinical perspective on the best, evidence-based medical options with the patient's individual circumstances, leaving the final decision to the patient. Further, it recognises respect for patient autonomy and helps physicians illuminate their own biases relative to what they deem to be the best course(s) of action through interaction with the patient [11].

Essential elements of SDM include: explanation of the health problem, presentation of available options and discussion of their benefits, risks and costs, assessment of patient values and preferences, discussion of patient's "own perceived ability to perform a specified behaviour or set of behaviors" and provision of recommendations, verification and clarification of patient's understanding, decision-making or deferral of decision, and arrangement of follow-up [12]. Multiple strategies and tools have been developed to foster and supplement the patient–physician relation and physician counselling. However, not all have been studied in the specific setting of organ donation and transplantation. Among these, patient decision aids (PDAs) – i.e. "interventions designed to help people make specific and deliberative choices among options (including the status quo) by making the decision explicit and by providing (at the minimum) information on the options and outcomes relevant to a person's health status" [13] – have been shown to be effective in improving patients' knowledge about available treatment options; in making them feel more informed and clearer about what is most important to them; in helping them have more accurate expectations of possible benefits and harms of their options; and in fostering more active participation in decision-making [14]. However, many other strategies and interventions have been put forward to improve informed consent and will be presented later in this chapter.

19.3. Communication of risk to transplant candidates

At the time of assessment for transplantation, patients are confronted with the choice of whether to pursue a transplant, to determine whether they will be able to manage the complexity of post-transplant requirements, to opt for a living (when applicable) or deceased donor and to consider a variety of options related to the potential for diminished graft quality (see §6.1.2 and Chapter 7) and donor risk profiles (see §6.1.1, Chapter 8, Chapter 9 and Chapter 10).

At the time of enrolment for transplantation, transplant candidates are provided with information about transplantation, and their consent to transplant should be ascertained through multiple discussions of the risks and benefits associated with the available options, culminating in the candidate's decision to accept or decline the offer of an organ. Studies suggest that these discussions should include the best available estimates of the patient's present and expected quality of life, along with information about mean waiting time based on blood type [15], the life expectancy of the average graft or the patient, the need for immunosuppression with its side effects and potentially adverse consequences such as cancer or infections, and other pertinent factors. Also, the risks associated with declining an organ offer and remaining on the waiting list must be presented [16] (see §6.1 and Table 19.4).

Therefore, prior to registration on transplant waiting lists, patients should be informed not only about the general risks of the surgical transplantation procedure, but also about the possibilities of disease transmission from donor to recipient. They should be advised that additional information or test results clarifying the risk of disease transmission may become available only after transplantation. In this case, transplant candidates must be reassured that, in the unlikely event of disease transmission, appropriate post-transplant testing, prevention and/or therapy will be offered to mitigate the risk or the severity of disease transmission. Additionally, candidates must be informed that there may be risks associated with a new outbreak of latent infectious diseases under immunosuppression, such as reactivation of *Cytomegalovirus* or other diseases. Discussions of complications due to immunosuppressive therapy are equally needed, since these can increase, particularly if enhanced immunosuppressive protocols (using mono- or polyclonal antibodies as induction therapy) are used.

19.3.1. Communication about organ quality and donor-related risks

The persistent discrepancy between demand and supply of organs for transplantation has encouraged the development of strategies aimed at expanding the donor pool. Expanded criteria donors (ECD) (see §6.1.3), non-standard risk donors (see §6.1.2), and donors after circulatory death (DCD) (see §6.1 and Chapter 12) are some examples. These pose new challenges to the informed consent process.

Several scholars have advocated the need to standardise the content, the way of communicating and the amount of information to be provided to patients at different time points of the transplant process so as to provide equal opportunities to wait-listed candidates [17, 18, 19].

Yet, variability in the timing and content of consent practices is widespread. A multicentre study across 35 European liver transplant centres found that 20 centres (65 %) provided information about ECDs to transplant candidates at the time of wait-listing, one (3 %) when an ECD liver became available and 10 (32 %) at both times. A special consent was requested of liver transplant candidates in 13 centres, whereas information on the donor's serology and donor's high-risk behaviours was given to potential recipients in 20 and 6 centres respectively [20]. One single-centre Dutch study of liver transplant candidates and recipients found that the risk of disease transmission that patients were willing to tolerate was 7 %, which rose to 12 % after receiving information about the rate of wait-list mortality. This finding was consistent across respondents, regardless of demographics or patient status (i.e. transplant *v.* wait-listed patients). Most wait-listed patients (between 59.8 % and 74.8 %) wished to be informed when there was an increased risk of infectious or malignant disease transmission, bile duct strictures and/or early graft failure. As for the preferred timing of when to receive information on donor-related risks, more than half of the patients wanted this to happen at the time of the organ offer; of these, more than 90 % wished to be involved in SDM [17]. Consistent with this, a previous study revealed that the vast majority (83 %) of wait-listed liver transplant candidates wanted to have an equal or dominant role in organ acceptance decisions [21]. Similarly, a study of kidney patients found that most patients (63 %) were willing to take part in the decisions regarding the quality of deceased donor kidneys [22]. Yet, research has shown that patients often have limited understanding of the different options and the corresponding outcomes relative to waiting list mortality, likelihood of transplant and organ quality [21, 23].

Patients' confusion about the distinction between issues of organ quality and increased infectious risks along with related concerns of infectious disease transmission (i.e. HIV, HBV, HCV), and desire for thorough information to make well-informed decisions have been previously reported in kidney transplant candidates [24]. Several studies have put forward the need to communicate risks in a way that is meaningful and easily comprehensible to the patient. A study of 332 written consent forms from 75 US transplant centres found that the vast majority of these were too difficult to read. Although it has been recommended that consent forms should be written at an average reading level of 5th to 8th grade (age 10 to 14), most were written at 'College Freshman' level (age 18) [25].

Some scholars suggest providing an actual quantification of risk, along with illustrative examples, so as to support both the patient's and the provider's decision making [18, 26]. Empirical research has demonstrated that PDAs are effective as another way to improve patient knowledge and decision making across different settings in organ transplantation. Studies found a significantly higher knowledge ($P < 0.001$) of transplantation in kidney transplant candidates who were exposed to PDAs [27, 28]. Also, significantly better knowledge of treatment options ($P < 0.001$), more accurate expectations about risks and benefits ($P < 0.001$), lower decision conflicts ($P = 0.0007$) and durable decisions ($P = 0.06$) were reported in a group of lung transplant candidates who benefited from a PDA as opposed to the usual care group [29]. As for liver transplant candidates, knowledge about HBV and HIV transmission significantly improved after exposure to a PDA, with a consequent higher awareness that they might be offered a less-than-perfect liver ($P = 0.001$) and a higher willingness to consider acceptance of such offer ($P < 0.001$) [30]. Other strategies have been implemented to improve patient understanding and decision-making capacity, both in the specific field of organ transplantation and in other areas of clinical practice (see Table 19.4).

While SDM is the most desirable model for decision making in medical care, a variety of factors may prevent it from being adopted in transplant clinical practice [31]. Among these factors, cross-centre variability in the criteria for defining ECDs [32, 33] and physicians' understanding of and attitudes to donor risks have been identified as potential contra-indications to SDM [15, 16]. Opponents of the use of SDM in the communication of organ quality and donor-related risks contend that discussion of risks and benefits at the time of the organ offer can be challenging given the limited time available for decision making. Donors may present individual risk factors that can be difficult to assess and explain in a timely, evidence-based manner to the transplant candidate. However, unilateral decision-making would be ethically unacceptable. Therefore, pre-emptive decision-making is generally advocated [11, 15, 31, 34].

Table 19.1. **Information to be given before enrolment on the transplant waiting list**

a. The screening process, including the information requested and investigations done prior to offering organs (see §6.2, §6.3, Table 6.4 and Chapter 12)

b. The information about the donor that may be shared with the recipient before or after transplantation (see Table 19.3)

c. The categories and types of donors and organs relevant to the individual (see §6.1, §6.1.1, §6.1.2, §6.1.3 and Chapter 12)

d. The risks associated with all organs and those that may derive from the varying characteristics of the donor (such as lifestyle, cause of death), from the organ itself and from the logistics of the transplant

e. The benefits of transplantation

f. The short- and long-term risks and implications of transplantation

g. The importance of long-term follow-up and relevant tests (which may include measurements of, for example, alcohol or illicit drugs), compliance with medical advice and need for immunosuppression

h. The consequences of non-transplantation

i. The possibility of and reasons for possible suspension or removal from the transplant waiting list

j. Explanation of the risks associated with:
- Organ transplantation
  - Risks of surgery (e.g. haemorrhage)
  - Donor factors signifying a risk of transmissible infectious disease (including *Cytomegalovirus*), malignancy or other conditions/diseases that may affect the health of the recipient (see §6.1.2, chapters 8, 9 and 10):
    - previous use of intravenous drugs
    - high-risk sexual behaviour
    - previous history of malignancy
    - residence in areas of some epidemic infections
  - Donor factors potentially affecting short- and long-term graft function (see §6.1.3 and Chapter 7)
    - age of donor
    - cause of death of donor
    - type of donor: DCD compared with DBD, the nature of the risk varying between organs (see chapters 6 and 12)
    - higher body mass index of donor
    - length of stay in an ICU prior to donation
    - split or reduced liver
    - longer warm and cold ischaemia times
- Immunosuppression:
  - Class-specific (e.g. increased risk of some *de novo* malignancies and infections)
  - Drug-specific (e.g. calcineurin inhibitor-associated renal impairment and diabetes)
- Risks of acute rejection (but with the high likelihood of response to treatment in most cases)
- Risks associated with transplantation (e.g. increased risk of cardiovascular disease)

k. The transplant candidate must be informed that specifying factors that are unacceptable in a donor organ will avoid the risks associated with a transplant using that organ but may put him/her at increased risk of dying before an 'acceptable' graft becomes available (see §6.1.1)

l. Patients must be informed that they will have the right to decline offered organs where there is evidence of significantly increased risk of either graft dysfunction or risk to the recipient's health (such as the transmission of infection)

m. Patients must be informed that, at the time of the organ offer, they may not be given all the information about the donor they request but will be informed if the donor is associated with a greater risk of transmission of infection or malignancy, or risk of non-function or greater technical complications. The potential recipient will not be informed of the reasons for the increased risk. It should also be anticipated that the following information will not be transmitted to the recipient at the time of the organ offer:
- name (or initials)
- occupation or social class
- date of birth
- place of donation
- ethnicity

The following information will only be transmitted to the recipient upon request
- sexual, alcohol or drug history

n. Transplant candidates must be informed that it is not often possible to quantify the degree of increased risk

o. Transplant candidates must acknowledge that not all the information requested may be available before a decision to accept or reject the offer is made and sometimes relevant information is available only after implantation

p. The potential recipient must be informed that no organ/donor/transplant is free of risk

Source: adapted from NHSBT/BTS. National Health Service Organ Donor Register. *Guidelines for consent for solid organ transplantation in adults*, 2015.

19.3.1.1. *Communication prior to enrolment on the transplant waiting list*

Multiple studies argue that discussion of the risks and benefits associated with different types of donor in relation to organ quality and risk of disease transmission should be initiated early in the process of assessment for transplantation, and periodically reiterated. Transplant candidates may experience a diminished quality of life or deterioration of their clinical condition and, in parallel, their willingness to accept non-standard risk donor organs or ECDs may vary over time [11, 18, 24, 31]. It is therefore advisable to explain the options and potential risks associated with accepting – or not accepting – an organ from a non-standard-risk donor or ECD at the time of listing for organ transplantation. At this time of the transplant process, an informed-consent form (written at 5th-8th grade/age 10-14 reading level) [25] must be signed by the transplant candidate, together with any additional specific informed-consent forms for ECDs, non-standard risk donors (infectious/malignant risk) or DCDs according to the patient's preferences. In order to ensure a comprehensive communication of the risks and benefits of transplantation to enable a more informed consent process, the NHS Blood and Transplant (NHSBT) and the British Transplantation Society (BTS) have jointly developed guidelines for consent for solid organ transplantation in adult patients [35], recommending that the

transplant candidate be given information about the aspects listed in Table 19.1.

19.3.1.2. *Maintaining consent while on the waiting list*

Depending on a variety of factors, time will likely elapse from enrolment on the transplant waiting list to transplantation itself. Therefore, the criteria under which a given recipient would/could accept an organ may change over time as a result of a change in their clinical and/or psychosocial condition. This is why it is important that recipient willingness to accept non-standard-risk donor organs, ECDs and/or DCDs should be re-evaluated regularly, particularly when there are changes in an individual's clinical status or diminished quality of life. Therefore, the time the candidate remains on the waiting list is not neutral [19], and the recommendation is to follow the NHSBT/BTS guidance [35] shown in Table 19.2.

Table 19.2. **Maintaining consent while on the waiting list**

a. The statement of consent includes confirmation that all the areas outlined previously have been covered by the transplant team and understood by the patient, or that the patient has consented to transplantation but explicitly requested not to be informed of the risks.
b. Clinicians should ensure that the patient awaiting a transplant remains aware of the risks and benefits of transplantation, especially when the patient's clinical condition changes and the balance of risks may be altered.
c. The patient should be advised to let the treating clinicians and transplant centres know if there is any material change to their position on consent in between formal reviews; this may arise if their condition deteriorates or if they wish for temporary suspension from the list.
d. Patients should be given the opportunity to review and revise their decisions for transplantation regularly and, where appropriate, the characteristics of the organ they would not wish to receive. The timing of such a review will depend on the condition of the patient and the type of transplant.
e. The patient needs to understand the importance of initiating a review if there is any non-medical change in their situation that is material to their consent.

Source: adapted from NHSBT/BTS, *Guidelines for consent for solid organ transplantation in adults*, 2015 [35].

19.3.1.3. *Communication at the time of the organ offer*

At the time of the organ offer, the specific, informed consent and the preferences of the recipient should be taken into account in the allocation procedure. Particularly, it is recommended to discuss with the recipient the donor information shown in Table 19.3, while avoiding revealing any details that might make the donor identifiable [34-36].

Table 19.3. **Discussion before final consent and acceptance of an organ**

a. Donor information (see Chapter 6, Chapter 7, Chapter 12): • Age range (by decade) • Gender • Type of death (such as trauma or cerebrovascular event) • Type of donor (DCD or DBD)
b. Whether the donor poses a greater risk of transmission of infection or malignancy. This applies when the transplant candidate has expressed willingness to accept these donor organ types previously. Other studies have stressed that, in this event, a special consent form must be signed by the potential recipient after the provision of the following information [34, 36]: • the infection(s) that may be transmitted and the likely risk of transmission • the potential severity of infection • the ease of treating the infection should transmission occur • whether all testing of the donor has been completed • the risk of significant morbidity and mortality without transplantation at this time • benefit of accepting this organ at this time [34] (see chapters 6 and 8) The same should be done in the presence of a greater risk of transmission of malignancy (see §6.1.2 and Chapter 9).
c. Whether the donor organ has a particular risk of poor function (such as acute tubular necrosis in a kidney; severe steatosis in a liver) and other factors potentially affecting short- and long-term graft function (see §6.1.2 and Chapter 7) • age of donor • cause of death of donor • type of donor: DCD compared with DBD, the nature of the risk varying between organs (see chapters 6 and 12) • higher body mass index of donor • length of stay in an ICU prior to donation • split or reduced liver • prolonged warm and cold ischaemia times
d. To respect the donor's anonymity, the following information should NOT be transmitted to the recipient either at the time of the organ offer or after transplantation: • name (or initials) • occupation or social class • date of birth • place of donation • ethnicity The following information should only be transmitted upon request • sexual, alcohol or drug history

Source: adapted from NHSBT/BTS. *Guidelines for consent for solid organ transplantation in adults*, 2015 [35].

Following transplantation, in the unlikely but potential event of infectious and/or malignant disease transmission, the decision about further action (e.g. graft removal and/or therapy) should be shared between the physician team and the recipient. Regarding communication and reporting of SAREs, see Chapter 16 for biovigilance issues and §19.5 for issues concerning communication to the broader public.

19.3.2. Communication strategies and tools to improve transplant candidate education or understanding and to enable shared decision making

Beyond the timing, content and details of the process of informed consent, throughout the different stages of the transplant process listed in this chapter, it is recommended that transplant programmes consider implementing communicative strategies to improve transplant candidate education and understanding, and to foster SDM [18, 25-31, 35, 37, 38] as in Table 19.4.

Table 19.4. **Communicative strategies to improve transplant candidate education and understanding, and to foster SDM**

a. Use a checklist to make sure that all the areas outlined throughout the previous sections have been covered by the transplant team both prior to enrolment on the waiting list (Appendix 28) and at the time of the organ offer (Appendix 29).
b. Risks should be explained in a manner that is best understood by the recipient and may include a mixture of diagrams and numeric illustrations.
c. The degree of risk associated with a particular transplant procedure or donor/organ type should be explained and illustrated against the risk of remaining on the waiting list and/or to forego transplantation – but avoid emotive terms for grafts (such as suboptimal, marginal, high risk).
d. The risks presented should be current and appropriate to the experience of the centre; national figures may be used where they are consistent with local data.
e. It is usually helpful to involve other members of the patient's family or friends in the education regarding transplantation and risk, particularly where co-morbidity in the recipient may impair comprehension.
f. Helpful for all transplant candidates and their family and friends to meet those who have already received a transplant. While this will give an incomplete picture of the procedure, it will help to understand and so lead to more informed consent.
g. Potential recipients should be provided with written educational material (written at 5th- to 8th-grade reading level) so as to allow understanding of the information provided.
h. Graphs, figures, and examples should be used to illustrate absolute risk estimates (avoid descriptive terms such as common, rare, possible, unlikely).
i. Balance relative risk with absolute risk and benefit (don't quote relative risk in isolation).
j. Personalise risk: data are derived for populations but need application to the individual.
k. Support the patient to evaluate available options based on their goals, preferences and concerns.
l. Use of electronic forms of communication (e.g. emails) to guarantee continuity of communication between patients and healthcare providers should be considered.
m. Where available, patient decision aids can be useful tools to supplement the process of informed consent and to foster shared decision-making.
n. Use of visual aids (e.g. a diagram depicting where the candidate is in the process of assessment for transplantation) should be employed to improve understanding.
o. Transplant candidates should be encouraged to ask questions of their physician team and should be empowered to do so. Providing patients with prompt question sheets can be a valuable support for them to make relevant questions about transplantation and stimulate discussions between patients and physicians (the U.S. Department of Health and Human Services [39] has a valuable example).
p. Interactive informed-consent interventions (i.e. those that intentionally promote active patient involvement and bidirectional communication), such as test/feedback and teach-back techniques, and digital interventions, can be an effective means to improve comprehension.
q. Implement interventions for patients with limited health literacy, limited numeracy, limited language proficiency, or visual or hearing impairments, and emphasise the use of qualified medical interpreters with working knowledge of transplantation.
r. Make communication tools and materials available in the patient's cultural and language preferences.

19.4. Communication of risk to living donors

Living donors (LD) are a unique group of healthy individuals who undergo elective surgery for the benefit of another person. The ethical and legal aspects, as well as issues relative to consent and authorisation for living donation have been addressed earlier in this Guide (see §13.2 and §13.3). As for transplant recipients, at the time of evaluation for kidney/liver donation, LDs must be informed that their consent to donation will unfold through (not just one, but) several discussions of the risks and benefits of living donation, culminating in the LD candidate's decision of whether or not to ultimately confirm their willingness to donate. Also, because some risks are uncertain or evolving, it is essential to embrace a long-term relationship with the LD, specifying that the process of living donation will not come to an end at the time of LD surgery [40].

Standardised informed-consent procedures should include surgical information (mortality and other major complications), medical information (minor complications, length of hospital stay, screening procedure, long-term effects of donation), psychosocial (risks of living with one kidney, follow-up, inflicted stress, depression, benefits, possible impacts on lifestyle), financial (expenses to be borne by donors, potential impact on ability to obtain life and health insurance, potential impact on ability to hold future employment) and other information (voluntary nature, legitimate ways out, recip-

ient benefits, risk of graft loss in recipient, alternative donation procedures, sick leave duration) [41].

19.4.1. Communication about risks and benefits of living donation

It is well established that consent must be voluntary, without coercion and fully informed. Studies suggest that the written and oral information provided to patients varies substantially across different countries and transplant centres. A study of 16 brochures used to inform live donor kidney transplant (LDKT) candidates and collected from 14 European and non-European centres found that some brochures met high standards whereas others were considered inadequate [42]. Similarly, a survey of transplant professionals in 177 transplant centres across 40 countries found considerable variation between countries and between centres in their risk communication and informed-consent process with LDKT candidates. Findings revealed that, although the majority of respondents informed potential donors about the increased risk of developing end-stage renal disease, the remaining 42 % said that there was no increased risk or avoided discussion of this risk completely. As for information about financial and psychosocial risks, most practitioners either minimised their likelihood or did not initiate discussion of these risks at all [43]. Similarly, a survey of transplant surgeons in the Netherlands found variations in consent practices for LDKT across centres and even among surgeons at the same centre. Communication of possible complications was inconsistent, with risk of death being always disclosed by only 50 % of respondents [44].

Similar findings are reported in living donor liver transplant (LDLT). A systematic review of US studies revealed that informed consent for LDLT is suboptimal because donors do not sufficiently appreciate the information received during the informed-consent process [45]. A survey of donor consent processes at 132 US kidney transplant programmes found large discrepancies in the types of risk disclosed. Half of the transplant programmes presumed consent for the donor evaluation [46]. A qualitative study of LDLT candidates equally found that their actual understanding of donation was inadequate, despite their subjective perception of having received satisfactory information [47]. Research suggests that LD candidates' understanding can be improved by supplementing the informed-consent processes with comprehension assessment tools, e-health educational tools and more comprehensible oral and written disclosure of information [25, 40, 41, 45, 47].

Although attaining a standardised consent format is virtually impossible given the heterogeneity of the LD pool and the differences in political, cultural and religious background between countries, several studies have advocated a standardised informed-consent process to offer equal educational and decision-making opportunities [41], psychosocial support and culturally sensitive informative material so as to prevent disparities across transplant centres [48, 49]. LD candidates must be provided with individually tailored quantitative estimates of short- and long-term risks associated with living donation and of its associated uncertainty in an easily understandable fashion [50]. Steiner *et al.* recommend providing the LD with visual aids describing absolute risks in a simple manner and using these to discuss the acceptable level of risk [51]. Voluntarism, medical suitability, benefits of LDKT for the recipient, risk of graft loss (together with assessments and estimates of the time likely to elapse before its potential occurrence), post-operative course, expected length of hospital stay following donation, short- and long-term medical and psychological risks, length of sick-leave, legal conditions and financial conditions have been put forward as critical elements of written consent forms to enable LD candidates to make thorough, well-informed decisions [42].

It is likely that some risks are easier to comprehend than others. Transplant centres often have data on their post-operative complications, and the surgical procedure and short-term risks are often well understood by donors [52]. Transplant centres should be encouraged to use their own data when counselling the patient rather than using generic international figures for post-operative complications and short-term risks. In the same study, only half of the donors understood the long-term medical risks. Long-term risks such as the risks of hypertension, pre-eclampsia and end-stage renal failure may be more difficult to understand and quantify, both for the potential donors, but also for the health professionals counselling the donor. Successful communication of these risks may be a demanding task for the transplant professional, and may require relevant training and skills, along with appropriate written information [53]. The distinction between relative and absolute risks is especially important for both the transplant professional and the potential donor when discussing risks [54]. Steiner has emphasised the importance of thorough donor education and informed consent before accepting a potential kidney donor [55]. This is even more important for donors with some type of isolated medical abnormality or from a population with high baseline risks of hyper-

tension or renal disease later in life. When informing younger donors about risks, it is important to describe the level of uncertainty regarding the long-term outcomes, since a normal donor evaluation is less predictive of future good health in younger individuals [56].

19.4.1.1. *Communication about risks and benefits of living donation prior to donor candidate evaluation*

Given the complexities inherent in the process of informed consent, it requires multiple discussions with transplant-experienced healthcare professionals to ensure LD candidate education and communica-

Table 19.5. **Recommended content of disclosure during the evaluation of living donor candidates**

Type of disclosure	Information disclosed to the donor candidate
a. Handling of donor candidate's personal health information	• Personal health information collected during the donor candidate evaluation is confidential and protected under privacy law, similar to other personal health information • The transplant programme will only disclose a donor candidate's personal health information to the intended recipient or other parties with the donor candidate's permission • The donor candidate may be asked for permission to disclose certain personal health information to their intended recipient. This information may include the donor candidate's identity, immunological compatibility and medical history affecting the risk of disease transmission
b. Risks of discovery of donor health information	• The programme's policy for disclosing information and arranging follow-up care for each of the following: – A health condition that may require further medical intervention – A health condition that could affect the donor candidate's ability to obtain insurance (e.g. life, medical, disability), or the cost of insurance – An infectious disease that must be reported to public health authorities – A misattributed biological relationship between the donor candidate and the intended recipient (such as misattributed paternity in a father–child relationship) discovered through blood group and immuno-compatibility testing
c. Risk and expected outcomes of donation	• The anticipated medical, surgical, psychosocial and economic risks and outcomes of donation, and the uncertainty in estimating risk and outcomes
d. Treatment alternatives available to transplant candidates	• Treatment options for kidney failure, including dialysis and deceased donor kidney transplantation, and their average expected outcomes compared with living kidney donor transplantation
e. Process of transplant candidate selection and when the intended recipient's personal health information is shared with the donor candidate	• Transplant candidate evaluation teams determine eligibility to receive a kidney transplant based on programme criteria and clinical judgment • Personal health information collected during the transplant candidate's evaluation is confidential, protected under privacy law, and is not generally shared with the donor candidate unless: • 1) the transplant programme determines that the donor candidate requires such information to make an informed decision about proceeding with donation, and • 2) the intended recipient gives permission for this information to be shared with the donor candidate
f. Processes of donor candidate evaluation, candidacy determination and follow-up	• Separate consents may be needed for some tests • Programmes and personnel available to help donors with the financial burden of donation • It may be a crime to receive any valuable consideration (money, property) for donation • A description of what will happen if the candidate decides not to donate, emphasising the right of the candidate to decline to donate at any time with the full support of the transplant programme • The transplant programme decision whether the donor candidate is eligible for donation based on the results of their evaluation • If excluded from donation, information on why the donor candidate does not meet the programme's criteria for donation and how the transplant programme will support the candidate • The programme's recommendations for follow-up care, including the timing and financial impacts of care and the need for regular, ongoing healthcare maintenance and healthy lifestyle choices • The programme's need to collect ongoing personal health information after donation to inform the care of the recipient, and to guide the care of the donor • The programme's policy on providing care to the donor after evaluation and donation • The availability of national and regional policies to assure prompt access to dialysis and transplantation for living donors who develop kidney failure

Source: KDIGO 2017 [40].

tion of risk, together with assessment of motivation, knowledge and understanding of the potential clinical and psychosocial outcomes of donation. These discussions must be initiated early and begin with the primary nephrologist, who should provide educational content and, in non-transplanting centres, refer transplant candidates and potential LDs to transplant centres for additional education and assessment [57]. According to the KDIGO clinical practice guideline on the evaluation and care of living kidney donors [40], it is recommended that these discussions should include disclosure of the information listed in Table 19.5 (for further details regarding LD screening, evaluation and medical and surgical risks specifically associated with LDKT and LDLT, refer to Chapter 13).

Table 19.6. **Recommended actions during the living donor evaluation process**

a. The treating physicians should ensure that all the aspects presented previously have been covered and that comprehension has been achieved by the donor.
b. Physicians should ascertain that the potential LD remains aware of the risks and benefits of donation.
c. The LD should be advised to inform the treating physicians about any change in their willingness to donate.
d. The LD should be reassured that they may withdraw from the evaluation process at any time and that the transplant programme will assist in communicating the decision to the intended recipient.
e. At the time of living donor surgery, the written informed consent of the donor must be obtained.

19.4.1.2. *Communication and actions during donor evaluation*

The process of evaluation allows time to elapse from the moment the LD candidate is informed about the opportunity to pursue living donation through to the time of donor surgery. This period serves multiple functions, allowing time for assessment of the LD's comprehension of the risks and benefits of the procedure and providing evidence of their actual, persistent motivation to pursue it. A survey of medical and surgical directors of kidney transplant programmes in the US found that only a minority of transplant programmes (11 %) require all potential LDs to exercise a so-called 'cooling-off' period to process all the information received during the informed-consent process. The majority either required a 'cooling-off' period only in selected cases (32 %) or did not require a 'cooling-off' period at all (57 %) [46]. Nevertheless, although the duration of the process is not defined and may vary based on the LD's individual characteristics, it is an essential requirement for valid informed consent.

Studies suggest that, in both LDKT and LDLT settings, the LD candidates' decision to donate occurs even before donor evaluation and educational processes are initiated [47, 58, 59]. A qualitative study of 28 LDLT candidates revealed that all donors, prior to receiving information on the risks associated with living donation, initially agreed and based their decision on emotions rather than logical reasoning. However, their first reaction of willingness to donate was followed by either:

a. a process of revision of their initial position after receiving more detailed information of the potential risks and outcomes of donation, or

b. avoidance of any reconsideration of these issues [60].

Table 19.7. **Communicative strategies and tools to enhance donor educational and decision-making processes**

a. The use of direct, simplified and repeated information may be helpful to facilitate comprehension.
b. Risk and outcome data should be transformed into easily understandable information using adult learning theory and health communication best practices.
c. Having potential donors speak with past donors who voluntarily consented to participate in donor education may help to increase understanding of the procedure.
d. Offer a list of reputable, comprehensive and up-to-date websites or consider development of own website for targeted education of potential donors.
e. The use of comprehension assessment tools or e-health educational tools will be helpful.
f. Use of specific cultural and linguistic competences in education may improve understanding in minority populations.
g. Repeat-back (e.g. asking the potential donor to reformulate the information received during the informed-consent process) and other health literacy methods which have proved effective in other areas of clinical practice may improve comprehension and enhance patient trust and the patient–physician partnership.
h. A living donor informed-consent checklist should be employed to ascertain that all the areas addressed in §19.4 and Chapter 13 are covered during the informed-consent process (Appendix 30).
i. LDs should be provided with a patient resource to explain the process in lay language. This resource should ideally be available in the living donor's native language (Appendix 31).
j. Consider use of motivational interviewing approaches to support potential LDs struggling with ambivalence throughout the evaluation process.
k. Culturally appropriate home visits and other home-based educational interventions may improve knowledge and reduce disparities in more vulnerable groups of patients.
l. Web-based portals and tools.
m. Support from family and friends.

Table 19.8. **Recommendations for risk communication to living donors that warrant formal study**

a. Provide the potential donor with a combination of verbal and written information.
b. Use plain language to make written and verbal materials more understandable.
c. Present data using absolute risk estimates.
d. Present information in pictographs if graphs are included.
e. Present data using frequencies.
f. Use an incremental risk format to highlight how post-donation risks change from pre-existing baseline levels.
g. Be aware that the order in which risks and benefits are presented can affect risk perceptions.
h. Consider use of summary tables to present all of the risks and benefits associated with donation.
i. Consider emphasising only the information that is most critical to the donor candidates' decision making, even at the expense of completeness.
j. Repeatedly draw the donor candidates' attention to the time interval over which a risk occurs.

Source: Lentine KL, Segev DL 2017 [50].

Similarly, a qualitative study of 30 LDLT candidates found that one third of the interviewed subjects were willing to receive thorough information with the aim of feeling more prepared for the procedure rather than for decision making itself [47]. LDs often base their decision to donate on the desire to help the recipient rather than on acknowledgment of the risks and benefits of the procedure [52]. However, other studies have shown that feelings of ambivalence (e.g. hesitation or uncertainty) are common among LDs and often go together with their intention to donate, with potential for inferior psychosocial outcomes following donation [61, 62].

Also, since there have been cases of infectious disease transmission from LD to recipient [63, 64], it is unclear whether LDs sufficiently appreciate their obligation to avoid behaviours that may put them at risk of acquiring infectious diseases prior to donation. Therefore, education of the LD on their behavioural risk factors that may be the cause of infectious disease transmission to the recipient are equally recommended (for further details refer to §13.7.1).

Based on the above premises, the time while the LD goes through multidisciplinary evaluations is critical for the LD candidate to acquire all the relevant information and discuss it with their transplant team. Particularly important recommendations are summarised in Table 19.6.

19.4.2. Communication strategies and tools to enhance decision making in living donor transplantation

In the same way as for the communication of risk to transplant recipients, it is recommended that specific communicative strategies and tools are used with living donors to enhance decision-making processes in LD transplant programmes [40, 45, 47, 65-78], as presented in Table 19.7 (see also Table 19.4 and Appendix 32).

In addition, based on recommendations for communication of risk developed in the general medicine and cancer literature, Lentine and Segev [50] have put forward a list of strategies that could be worth testing among LDs (Table 19.8).

19.5. Crisis management and communication in the event of serious adverse reactions and/or events

The risks associated with deceased donor and living donor transplantation have been extensively presented throughout this chapter and elsewhere in this Guide. The risk of disease transmission to a recipient as a result of transplantation, the death of a recipient or a living donor, and other SAREs (for definition and further details of SAREs, see Chapter 16) remain very rare yet inevitable events in the working field of organ transplantation. These aspects hold significant potential for crises, although at unpredictable points in time. Coombs describes crises as "unusual occurrences that cannot be predicted but are expected", and stresses that no organisation is entirely exempt from the occurrence of such events, even when the degree of vigilance is high [79]. Consistent, prior studies on LDLT highlight that, in this specific area, it is not a matter of determining if the death of a living liver donor will ever occur but, rather, when it will occur [80].

Many different definitions can be found for the term 'crisis'. According to Heath,

> a crisis is typically defined as an untimely but predictable event that has actual or potential consequences for stakeholders' interests as well as the reputation of the organization. … That means a crisis can harm stakeholders and damage the organization's relationship with them. … Respond well and survive the crisis; respond poorly and suffer the death of the organization's reputation and perhaps itself. [81]

Table 19.9. **Pre-crisis, crisis response and post-crisis: best practices**

Pre-crisis	
Crisis prevention	a. Develop systems aimed at detecting, locating and tracking potential risks for future crises.
Crisis management preparation	a. Have a crisis management plan and update it at least annually. b. Have a designated crisis-management team that is properly trained. c. Conduct an exercise at least annually to test the crisis-management plan and team. d. Pre-draft select crisis-management messages, including content for dark web sites and templates for crisis statements. Have the legal department review and pre-approve these messages.
Crisis	
Response to a definite event	a. Be quick and try to have initial response within the first hour. b. Be accurate by carefully checking all facts. c. Be consistent by keeping spokes-people informed of crisis events and key message points. d. Make public safety the number one priority. e. Use all of the available communication channels, including the internet, intranet and mass notification systems. f. Provide some expression of concern/sympathy for victims (see §19.5.3). g. Remember to include employees in the initial response. h. Be ready to provide stress and trauma counselling to victims of the crisis and their families, including employees.
Post-crisis	
Learning from a crisis event	a. Deliver all information promised to stakeholders as soon as that information is known. b. Keep stakeholders updated on the progression of recovery efforts including any corrective measures being taken and the progress of investigations. c. Analyse the crisis management effort for lessons and integrate those lessons into the organisation's crisis management system.

Source: adapted from IRP, 2007 [83]

This definition highlights the importance of crisis management as a critical element to preserve the relationship with stakeholders, the organisation's reputation, and trust towards the organisation.

Crisis management has been defined as "a set of factors designed to combat crises and to lessen the actual damages inflicted" to "prevent or lessen the negative outcomes of a crisis and thereby protect the organization and its stakeholders … from damage" [79]. Given that crises are expected in certain areas, there is general agreement that the ability to prepare for the inevitable is a critical quality of any successful organisation. Crisis management should, therefore, be an ongoing process rather than an isolated measure to counter an SARE [79, 80, 82]. According to Coombs, the set of factors that compose crisis management can be grouped into three distinct categories that correspond with the actual phases of the crisis management agenda, namely 1. pre-crisis, 2. crisis response, and 3. post-crisis [79]. The leading priority of the pre-crisis phase is prevention, along with preparation. The crisis response phase is when management and communication actually need to respond to a crisis, and the post-crisis phase seeks to identify elements for improvement in preparing for the next crisis and fulfils commitments undertaken during the crisis phase, including delivery of follow-up information (Table 19.9).

Research on crisis management plans (CMPs) in the specific field of organ donation and transplantation remains scarce. General indications on crisis communication when unanticipated events occur in the process of organ donation and transplantation have been put forward by Van der Laan within the project Foedus (Facilitating Exchange of Organs Donated in EU Member States) [84], whereas other writers focus more specifically on CMPs in living donor programmes [80, 85].

19.5.1. General indications on crisis communication in the process of organ donation and transplantation

Good crisis communication is a critical element of successful CMPs. Not having a pre-established, clear, crisis communication policy and approach in place at the time an unforeseen event happens adds complexity and represents an additional crisis that an organisation needs to manage. Studies show that organisations who respond in a professional fashion to a crisis are rewarded by their stakeholders and maintain trust, whereas those who are unprepared, react late and/or provide incomplete responses (e.g. 'no comment') to the media do not. Therefore, in the specific context of organ donation and transplantation, the pre-crisis phase should be initiated long before the actual occurrence of an SARE.

Communication in the event of a crisis is a unique challenge for an organisation. It requires specific expertise that should be delegated to a spe-

cialised, well-trained team within the organisational structure.

Van der Laan [84] proposes a model for crisis communication divided into three distinct phases, culminating in the communication with stakeholders, the media and the public (Table 19.10).

Table 19.10. **Stages and elements of the crisis-response phase**

Stage 1: Information, scenarios, organisation
• Draw the landscape: what is happening here? • Define the position: what is our role/responsibility in this situation? • Appoint a team of specialists (e.g. experts, spokesperson)
Stage 2: Image, assessment, decision-making
• Fully agree about the situation and expectations (scenarios) • Decide on the communication strategy: proactive/reactive and key principles
Stage 3: Communicate with stakeholders, the media, the public
• Make use of various communication tools: web, social media, email, phone • Act according to key communication principles • Continuous media monitoring: (tweetdeck) – what is said/written about this topic • Make a time schedule for your communication moments: be aware of the principle 'informed waiting reduces stress'

Source: adapted from Van der Laan J. 2016 [84].

During Stage 3, it is recommended to apply the following guidelines [84]:

a. Accuracy before speed.
b. High level of availability for the media – informed waiting reduces stress.
c. Support journalists to bring them into contact with the 'right' persons.
d. Keep control: the timing of your press releases.
e. Constantly check the stages: new information, new decisions?
f. Co-operate with other parties (authorities).
g. Always keep your employees informed.

19.5.2. Crisis-management plans in living donor programmes

The post-operative risk of mortality for LDs is extremely low; yet, it is not zero. The death of an LD is a tragic and overwhelming event not only for the LD's family but also for the recipient, clinical team and transplant programme. A survey of US living kidney donor (LKD) (n = 76) and living liver donor (LLD) (n = 17) transplant surgeons, representing 87 unique transplant programmes, revealed that most respondents were concerned about either LKDs' or LLDs' deaths. However, the majority (68 %) reported that their organisation does not have a CMP in the event of an LD's death. Based on an earlier study on crisis management in the event of an LLD's death [80], and incorporating elements from transplant programmes that do have CMPs, the authors have built an outline of talking points to guide individual transplant programmes' development of Living Donor Crisis Management Plans (Table 19.11) [85].

According to Henderson *et al.* [85], the first part of the CMP should primarily state its purpose and scope, including clarification of roles, design of communication plans and definitions of action steps throughout the three phases of the crisis management agenda. Team participation should be promoted, and senior institutional leadership should be included. Also, CMPs should consider that, in the event of a donor crisis, the needs of the different stakeholders may be competing relative to internal and external response and message delivery. Revision of CMPs should equally be scheduled annually.

The pre-crisis phase should be aimed at outlining practices for donor safety and advocacy so as to effectively prevent the potential for adverse events by drawing attention to processes. Donor safety assets should be personalised depending on the protocols of individual transplant programmes. Yet, they may include independent living donor advocacy (ILDA) to support informed consent processes, peri-operative checklists, well-defined staffing and monitoring procedures, and a communication escalation protocol.

In the event of a crisis, precise definition of team roles and communication tasks are critical for successful management of the crisis itself. In the first place, quick, accurate and consistent communication should be directed to internal and external stakeholders. Members, roles, hierarchy and a communication pathway should be defined, and ILDAs should be included. Templated messages and a well-trained spokesperson are recommended. Given that the donor surgeon may be essential to primary donor family communication, it is equally recommended to remove him/her from managing the crisis.

The post-crisis phase is concerned with long-term consequences to the programme and is aimed at gradually returning to normal activities. In this phase, designated clinicians should be identified for communication with the LD's family and the recipient. A communication plan for the clinical care team is also suggested along with supportive care, and a schedule for crisis management team meetings. Programme leadership should co-ordinate reporting to national health authorities (for further details on re-

porting, see §16.4.2), perform a root-cause analysis and develop corrective action plans. A plan to follow up on commitments made during the crisis phase (e.g. release of updates) to the public or to affected families is also recommended.

19.5.3. Duty of Candour

Provision of healthcare services is associated with risks and, from time to time, there are unintended or unexpected events that result in death or harm. When this happens, people want to be told honestly what happened, what will be done in response and that improvements will be made to prevent this from happening again.

All health professionals and healthcare organisations have a Duty of Candour (DoC), which ensures that they are open, honest and supportive with patients and their relatives about all elements of their care and treatment and when there are unexpected or unintended incidents resulting in harm or death.

An event which activates the DoC may fall in any of the following categories:

a. death of the person,
b. a permanent lessening of bodily, sensory, motor, physiologic or intellectual functions,
c. an increase in the person's treatment,
d. changes to the structure of the person's body,
e. the shortening of the life expectancy of the person,
f. an impairment of the sensory, motor or intellectual functions of the person which has lasted, or is likely to last, for a continuous period of at least 28 days,
g. the person experiencing pain or psychological harm which has been, or is likely to be, experienced by the person for a continuous period of at least 28 days,
h. the person requiring treatment by a registered health professional in order to prevent:
- the death of the person, or
- any injury to the person which, if left untreated, would lead to one or more of the outcomes mentioned above.

DoC will require healthcare organisations and workers to:

a. notify the person affected of the event (and/or family/relative if appropriate),
b. provide an apology,
c. carry out a review into the circumstances leading to the event,
d. offer and arrange a meeting with the person (and/or family/relative if appropriate),

Table 19.11. **Living donor crisis management plan, talking points**

a. Introduction	• Statement of purpose and scope – Define crisis events (for definitions of SAREs, see §16.2, Table 16.1) • Describe process to build plan – Inclusive of team members and senior institutional leadership – Consideration of stakeholders that may have competing needs – Schedule for review/revision annually
b. Pre-crisis phase	• Outline safety fundamentals that help prevent donor catastrophe – Delineate robust staffing and monitoring procedures – Describe communication escalation protocol with defined clinical chain of command – Donor advocacy that supports informed consent process (ideally a donor advocate team)
c. Crisis phase	• Describe crisis-management team – Identify key personnel roles – Define specific responsibilities, chain of command and chain of communication – Include senior institutional leadership – Invite ILDA • Plan for quick, accurate, consistent messaging – Template messages – Train spokesperson – Remove donor primary surgeon from crisis management
d. Post-crisis phase	• Communication plan – Designate clinician to communicate with donor family, and with recipient – Implement communication plan with clinical care team – Provide supportive care for donor team • Address consequences and gradually resume normal activities – Reporting (for further details see §16.4.2) – Root cause analysis – Corrective action planning • Define schedule for crisis management team meetings (suggested daily huddle)

Source: adapted from Henderson *et al.* 2020 [85].

e. provide the person affected with an account of the event,
f. provide information about further steps taken,
g. make available, or provide information about, support for persons affected by the event,
h. prepare and publish an annual report on the DoC (organisations).

19.5.3.1. *Identifying events that trigger Duty of Candour*

In most cases, adverse events that would trigger the DoC procedure will be identified as part of an established process for managing adverse events. This may be evident at the time of the event, or it may not be apparent until a review has been carried out. A small number, however, may be identified through other processes, such as complaints or morbidity and mortality reviews, which through review or investigation identify that harm has been caused to an individual during the course of their care or treatment. Organisations must have a clear process in place to deliver the DoC and engage with the patient/family. It is essential that this happens in a timely manner following the event.

19.5.3.2. *Supporting patients and families*

The first consideration following an adverse event is that the patient must be cared for, their health and well-being secured, and further risk mitigated. The patient's family must be involved when a patient has died or suffered serious harm.

Where an adverse event has a direct impact on a patient, it should be discussed with them by the most appropriate member of the clinical team as soon as is practical. Information and support to the patient and relatives should be provided, including information on support systems available. Compassion and understanding should be demonstrated at all times, and arrangements for ongoing contact should be agreed with the patient/family to keep them informed of the progress of reviews and/or improvement plan implementation.

When patients and families are affected by adverse events, organisations should demonstrate transparency and openness and give an apology. Saying sorry is not an admission of liability, but is an understanding of the distress or worry experienced.

The Institute for Healthcare Improvement (IHI) [86] suggests that an adverse event does not necessarily break down the trust between patient and staff; however, the way in which the organisation responds after such events often does.

Open communication about adverse events is part of good clinical practice and not something separate which is initiated when an adverse event occurs. 'Being open' is a process of actions and behaviours, and it requires a culture that visibly encourages key behaviours, including:

- honesty,
- openness,
- appropriate sharing of information,
- a willingness to learn from experience and to change how the organisation functions.

19.6. Conclusion

Informed consent is a legal and ethical requirement in the working field of organ donation and transplantation. It is a complex process and a critical element to guarantee safety and quality across the lifelong continuum of care of transplantation and living donation. Active transplant candidate/recipient/LD participation is the cornerstone to enable SDM as the most desirable model for decision making in clinical practice. In communicating benefits and risks to transplant and/or LD candidates, physician teams should ensure that proper communication strategies and tools are in place to enhance the patient–physician partnership, to perform thorough educational interventions to improve knowledge of transplant and/or donation, to assess comprehension, motivation, views and preferences among the multiple options and aspects inherent in transplantation. In order to prevent disparities between transplant centres, the timing, content, details and modality of information and education for the transplant candidate, recipient and LD should combine a certain degree of standardisation with the need to provide an individualised, patient-centred approach to care.

Research agenda

1 Studies have shown that variability exists in the timing, content, details and modality of information and education for transplant candidates, recipients and LDs across transplant centres in Europe and elsewhere. However, studies are needed to assess how informed-consent processes for transplant and donor candidates are currently performed in transplant centres in Europe. Additionally, much remains to be investigated as to the most effective strategies to enhance the patient–physician partnership, improve comprehension and assess recipients' and LDs' understanding of the risks and benefits of transplantation or living donation.
2 In particular, it remains unclear whether younger LDs sufficiently appreciate the level of uncertainty about the long-term outcomes of living donation, since regular LD evaluations are less predictive of future expected outcomes in this group of patients. Assessment of working practices for communication

of risk to younger LDs across European transplant programmes is needed, along with studies aimed at the development of strategies for effective communication and testing of comprehension.

3 Also, communication of risk in the European context to more vulnerable groups of patients or LDs (i.e. socio-economically disadvantaged subjects, individuals who have migrated from other countries, who are from ethnic minorities or who have a different first language, patients with limited health literacy, elderly persons and other vulnerable categories) requires further investigation. This will allow determination of the requirement for targeted strategies to accommodate the needs of these vulnerable patients and guarantee provision of high-quality care throughout the transplantation and/or living donation process. More evidence is needed regarding the clinical and psychosocial outcomes resulting from the use of specific communicative strategies and tools to supplement and enhance informed consent and educational processes. Multiple solutions have been developed to supplement and enhance the processes of informed consent and patient education in other fields of clinical practice. Studies are needed to assess the effectiveness of these practices in the specific field of transplantation and living donation.

4 Research on communicative strategies and decision making about actions in the event of malignant and/or infectious disease transmission is also lacking.

5 It has also been shown that research on CMPs and crisis communication remains limited in Europe. Future studies should develop more robust indications to guide the development of CMPs for deceased and living donor transplant programmes across Europe.

19.7. References

1. Aggarwal VB, Gupta V. *Handbook of journalism and mass communication*. New Delhi: Concept Publishing, 2002.
2. Barry MJ, Edgman-Levitan S. Shared decision making – the pinnacle of patient-centered care. *N Engl J Med* 2012;366(9):780-1.
3. Elwyn G, Laitner S, Coulter A *et al.* Implementing shared decision making in the NHS. *BMJ* 2010; 341(7780):971-2.
4. Grad R, Légaré F, Bell NR *et al.* Shared decision making in preventive health care: what it is; what it is not. *Can Fam Physician* 2017;63(9):682-4.
5. UNESCO. *Report of the International Bioethics Committee of UNESCO (IBC) on consent* [Internet], 2008 [cited 23 Jan 2021], available at http://unesdoc.unesco.org/images/0017/001781/178124e.pdf, accessed 27 July 2021.
6. Brenner LH, Brenner AT, Horowitz D. Beyond informed consent: educating the patient. *Clin Orthop Relat Res*. 2009;467(2):348-351. DOI:10.1007/s11999-008-0642-4.
7. Whitney SN, McGuire AL, McCullough LB. A typology of shared decision making, informed consent, and simple consent. *Ann Intern Med* 2004;140(1):54-9.
8. Shay AL, Lafata JE. Where is the evidence? A systematic review of shared decision making and patient outcomes. *Med Decis Mak* 2015;35(1):114-31.
9. Joosten EAG, DeFuentes-Merillas L, De Weert GH *et al.* Systematic review of the effects of shared decision-making on patient satisfaction, treatment adherence and health status. *Psychother Psychosom* 2008;77(4):219-26.
10. Kaplan RS, Haas DA, Warsh J. Adding value by talking more. *N Engl J Med* 2016;375(20):1918-20.
11. Ross LF, Zenios S, Thistlethwaite JR. Shared decision making in deceased-donor transplantation. *Lancet* 2006;368(9532):333-7.
12. Makoul G, Clayman ML. An integrative model of shared decision making in medical encounters. *Patient Educ Couns* 2006;60(3):301-12.
13. Stacey D, Bennett CL, Barry MJ *et al.* Decision aids for people facing health treatment or screening decisions. *Cochrane Database Syst Rev* 2011 Oct 5;10:CD001431.
14. Stacey D, Légaré F, Lewis K *et al.* Decision aids for people facing health treatment or screening decisions. *Cochrane Database Syst Rev* 2017 Apr 12;4(4): CD001431.
15. Reese PP, Tehrani T, Lim MA *et al.* Determinants of the decision to accept a kidney from a donor at increased risk for blood-borne viral infection. *Clin J Am Soc Nephrol* 2010;5(5):917-23.
16. Halpern SD, Shaked A, Hasz RD, Caplan AL. Informing candidates for solid-organ transplantation about donor risk factors. *N Engl J Med* 2008;358(26): 2832-7.
17. Op Den Dries S, Annema C, Berg APV Den *et al.* Shared decision making in transplantation: how patients see their role in the decision process of accepting a donor liver. *Liver Transpl* 2014;20(9):1072-80.
18. Moayedi Y, Ross HJ, Khush KK. Disclosure of infectious risk to heart transplant candidates: shared decision-making is here to stay. *J Heart Lung Transplant* 2018;37(5):564-7.
19. Grossi AA, Nicoli F, De Feo TM *et al.* The 3-T Model of Informed Consent for Non-Standard Risk Donors: a proposal for transplant clinical practice. *Transplant Direct* 2021 Oct 22;7(11):e782. https://doi.org/10.1097/TXD.0000000000001238.
20. Bruzzone P, Giannarelli D, Adam R. A preliminary European Liver and Intestine Transplant Association–European Liver Transplant Registry study on informed recipient consent and extended criteria liver donation. *Transplant Proc* 2013;45(7):2613-15.

21. Volk ML, Tocco RS, Pelletier SJ *et al.* Patient decision making about organ quality in liver transplantation. *Liver Transpl* 2011;17(12):1387-93.
22. van Hoogdalem LE, Hoitsma A, Timman R *et al.* Shared decision-making in kidney patients: involvement in decisions regarding the quality of deceased donor kidneys. *Transplant Proc* 2018;50(10):3152-9.
23. Hart A, Bruin M, Chu S *et al.* Development of an individualized online shared decision making tool for kidney transplant candidates. *Am J Transplant* 2018; 17(Suppl 3), available at https://atcmeetingabstracts.com/abstract/development-of-an-individualized-online-shared-decision-making-tool-for-kidney-transplant-candidates/, accessed 19 January 2022.
24. Gordon EJ, Reddy E, Ladner DP *et al.* Kidney transplant candidates' understanding of increased risk donor kidneys: a qualitative study. *Clin Transplant* 2012;26(2):359-68.
25. Gordon EJ, Bergeron A, McNatt G *et al.* Are informed consent forms for organ transplantation and donation too difficult to read? *Clin Transplant* 2012;26(2):275-83.
26. Kucirka LM, Singer AL, Segev DL. High infectious risk donors: what are the risks and when are they too high? *Curr Opin Organ Transplant* 2011;16(2):256-61.
27. Axelrod DA, Kynard-Amerson CS, Wojciechowski D *et al.* Cultural competency of a mobile, customized patient education tool for improving potential kidney transplant recipients' knowledge and decision-making. *Clin Transplant* 2017 May;31(5). DOI:10.1111/ctr.12944.
28. Patzer RE, McPherson L, Basu M *et al.* Effect of the iChoose Kidney decision aid in improving knowledge about treatment options among transplant candidates: a randomized controlled trial. *Am J Transplant* 2018;18(8):1954-65.
29. Vandemheen KL, O'Connor A, Bell SC *et al.* Randomized trial of a decision aid for patients with cystic fibrosis considering lung transplantation. *Am J Respir Crit Care Med* 2009;180(8):761-8.
30. Volk ML, Roney M, Fagerlin A. Pilot test of a patient decision aid about liver transplant organ quality. *Liver Transpl* 2014;20(7):850-5.
31. Gordon EJ, Butt Z, Jensen SE *et al.* Opportunities for shared decision making in kidney transplantation. *Am J Transplant* 2013;13(5):1149-58.
32. Bruzzone P, Giannarelli D, Nunziale A *et al.* Extended criteria liver donation and transplant recipient consent: The European experience. *Transplant Proc* 2011; 43(4):971-3.
33. Bruzzone P, Balla A, Quaresima S *et al.* Comparison of two questionnaires on informed consent in 'marginal' donor liver. *Transplant Proc* 2016;48(2):359-61.
34. White SL, Rawlinson W, Boan P *et al.* Infectious disease transmission in solid organ transplantation: donor evaluation, recipient risk, and outcomes of transmission. *Transplant Direct* 2019;5(1):e416.
35. NHSBT/BTS. Policy POL191/2 *Guidelines for consent for solid organ transplantation in adults*, 2015, available at https://nhsbtdbe.blob.core.windows.net/umbraco-assets-corp/4378/guidelines_consent_for_solid_organ_transplantation_adults.pdf, accessed 27 July 2021.
36. Ison MG, Nalesnik MA. An update on donor-derived disease transmission in organ transplantation. *Am J Transplant* 2011;11(6):1123-30.
37. The Joint Commission. Informed consent: more than getting a signature. Quick Safety [internet] Feb 2016;21, available at www.jointcommission.org/-/media/deprecated-unorganized/imported-assets/tjc/system-folders/joint-commission-online/quick_safety_issue_twenty-one_february_2016pdf.pdf?db=web&hash=5944307ED39088503A008A70D2C768AA, accessed 27 July 2021.
38. Glaser J, Nouri S, Fernandez A *et al.* Interventions to improve patient comprehension in informed consent for medical and surgical procedures: an updated systematic review. *Med Decis Mak* 2020;40(2):119-43.
39. U.S. Department of Health and Human Services. *Partnering with Your Transplant Team. The Patient's Guide to Transplantation* [internet]. Rockville MD: Health Resources and Services Administration, Healthcare Systems Bureau, Division of Transplantation; 2008, available at https://unos.org/wp-content/uploads/unos/PartneringWithTransplantTeam.pdf, accessed 27 July 2021.
40. Lentine KL, Kasiske BL, Levey AS *et al.* KDIGO clinical practice guideline on the evaluation and care of living kidney donors. *Transplantation* 2017;101(8): S1-109.
41. Kortram K, Lafranca JA, IJzermans JNM, Dor FJMF. The need for a standardized informed consent procedure in live donor nephrectomy: a systematic review. *Transplantation* 2014;98(11):1134-43.
42. Lennerling A, Nyberg G. Written information for potential living kidney donors. *Transpl Int* 2004;17(8): 449-52.
43. Parekh AM, Gordon EJ, Garg AX *et al.* Living kidney donor informed consent practices vary between US and non-US centers. *Nephrol Dial Transplant* 2008; 23(10):3316-24.
44. Kortram K, Ijzermans JNM, Dor FJMF. Towards a standardized informed consent procedure for live donor nephrectomy: what do surgeons tell their donors? *Int J Surg* 2016;32:83-8.
45. Gordon EJ, Daud A, Caicedo JC *et al.* Informed consent and decision-making about adult-to-adult living donor liver transplantation: a systematic review of empirical research. *Transplantation* 2011;92(12):1285-96.

46. Rodrigue JR, Pavlakis M, Danovitch GM *et al.* Evaluating living kidney donors: relationship types, psychosocial criteria, and consent processes at US transplant programs. *Am J Transplant* 2007;7(10): 2326-32.
47. Gordon EJ, Rodde J, Skaro A, Baker T. Informed consent for live liver donors: a qualitative, prospective study. *J Hepatol* 2015;63(4):838-47.
48. Hanson CS, Chadban SJ, Chapman JR *et al.* Nephrologists' perspectives on recipient eligibility and access to living kidney donor transplantation. *Transplantation* 2016;100(4):943-53.
49. Timmerman L, Ismail SY, Luchtenburg AE *et al.* Exploring knowledge about dialysis, transplantation, and living donation among patients and their living kidney donors. *Int J Behav Med* 2015;22(5):580-9.
50. Lentine KL, Segev DL. Understanding and communicating medical risks for living kidney donors: a matter of perspective. *J Am Soc Nephrol* 2017;28(1):12-24.
51. Steiner RW, Gert B. A technique for presenting risk and outcome data to potential living renal transplant donors. *Transplantation* 2001;71(8):1056-7.
52. Valapour M, Kahn JP, Bailey RF, Matas AJ. Assessing elements of informed consent among living donors. *Clin Transplant* 2011;25(2):185-90.
53. Lapointe Rudow D, Hays R, Baliga P *et al.* Consensus conference on best practices in live kidney donation: recommendations to optimize education, access, and care. *Am J Transplant* 2015;15(4):914-22.
54. Serur D, Gordon EJ. Kidney donors at risk: how to inform the donor. *Prog Transplant* 2015;25(4):284-6.
55. Steiner RW. Risk appreciation for living kidney donors: another new subspecialty? *Am J Transplant* 2004;4(5):694-7.
56. Steiner RW. 'Normal for now' or 'at future risk': a double standard for selecting young and older living kidney donors. *Am J Transplant* 2010;10(4):737-41.
57. Tan JC, Gordon EJ, Dew MA *et al.* Living donor kidney transplantation: facilitating education about live kidney donation – recommendations from a consensus conference. *Clin J Am Soc Nephrol* 2015;10(9): 1670-7.
58. Fellner CH, Marshall JR. Kidney donors – the myth of informed consent. *Am J Psychiatry* 1970;126(9):1245-51.
59. Lennerling A, Forsberg A, Nyberg G. Becoming a living kidney donor. *Transplantation* 2003;76(8):1243-7.
60. Papachristou C, Marc W, Frommer J, Klapp BF. Decision-making and risk-assessment in living liver donation: how informed is the informed consent of donors? A qualitative study. *Psychosomatics* 2010; 51(4):312-19.
61. Shenoy A. The psychosocial evaluation of live donors. In: *Psychosocial care of end-stage organ disease and transplant patients*. Cham, Switzerland: Springer International; 2019, pp. 49-59.
62. DiMartini A, Cruz RJ, Dew MA *et al.* Motives and decision making of potential living liver donors: comparisons between gender, relationships and ambivalence. *Am J Transplant* 2012;12(1):136-51.
63. HIV transmitted from a living organ donor – New York City, 2009. *Am J Transplant* 2011;11(6):1334-7.
64. Centers for Disease Control and Prevention (CDC). HIV transmitted from a living organ donor – New York City, 2009. *Morb Mortal Wkly Rep* 2011;60(10): 297-301.
65. Abramowicz D, Cochat P, Claas FHJ *et al.* European renal best practice guideline on kidney donor and recipient evaluation and perioperative care. *Nephrol Dial Transplant* 2015;30(11):1790-7.
66. OPTN. *OPTN Living Donor Informed Consent Checklist* [Internet], 2017, available at https://optn.transplant.hrsa.gov/media/2162/living_donor_consent_checklist.pdf, accessed 27 July 2021.
67. White CS, Mason AC, Feehan M, Templeton PA. Informed consent for percutaneous lung biopsy: comparison of two consent protocols based on patient recall after the procedure. *Am J Roentgenol* 1995;165(5): 1139-42.
68. Fink AS, Prochazka AV. Henderson WG *et al.* Enhancement of surgical informed consent by addition of repeat back: a multicenter, randomized controlled clinical trial. *Ann Surg* 2010;252(1):27-36.
69. Agency for Healthcare Research and Quality (AHRQ). *The SHARE Approach – Using the teach-back technique: a reference guide for health care providers*. AHRQ, available at www.ahrq.gov/health-literacy/professional-training/shared-decision/tool/resource-6.html, accessed 27 July 2021.
70. Garonzik-Wang JM, Berger JC, Ros RL *et al.* Live donor champion: finding live kidney donors by separating the advocate from the patient. *Transplantation* 2012;93(11):1147-50.
71. Gordon EJ, Caicedo JC, Ladner DP *et al.* Transplant center provision of education and culturally and linguistically competent care: a national study. *Am J Transplant* 2010;10(12):2701-7.
72. Dew MA, Dimartini AF, Devito Dabbs AJ *et al.* Preventive intervention for living donor psychosocial outcomes: feasibility and efficacy in a randomized controlled trial. *Am J Transplant* 2013;13(10):2672-84.
73. Rodrigue JR, Pavlakis M, Egbuna O *et al.* The 'house calls' trial: a randomized controlled trial to reduce racial disparities in live donor kidney transplantation: rationale and design. *Contemp Clin Trials* 2012;33(4): 811-18.
74. Ismail SY, Luchtenburg AE, Timman R *et al.* Home-based family intervention increases knowledge,

communication and living donation rates: a randomized controlled trial. *Am J Transplant* 2014;14(8): 1862-9, available at https://onlinelibrary.wiley.com/doi/full/10.1111/ajt.12751, accessed 27 July 2021.

75. Gordon EJ, Ladner DP, Caicedo JC, Franklin J. Disparities in kidney transplant outcomes: a review. *Semin Nephrol* 2010;30(1):81-9.
76. Gordon EJ, Feinglass J, Carney P *et al.* A culturally targeted website for hispanics/latinos about living kidney donation and transplantation: a randomized controlled trial of increased knowledge. *Transplantation* 2016;100(5):1149-60.
77. Fisher RA. Enabling altruism: evaluating the adult living liver donor. *Liver Transpl* 2007;13(4):478-9.
78. Gordon EJ, Mullee J, Butt Z *et al.* Optimizing informed consent in living liver donors: evaluation of a comprehension assessment tool. *Liver Transpl* 2015 Oct;21(10):1270-9.
79. Coombs WT. Parameters for crisis communication. In: WT Coombs, SJ Holladay, eds. *The handbook of crisis communication* [Internet]. Oxford, UK: Wiley-Blackwell, 2010, pp. 17-53, available at http://doi.wiley.com/10.1002/9781444314885.ch1, accessed 27 July 2021.
80. Miller C, Smith ML, Fujiki M *et al.* Preparing for the inevitable: the death of a living liver donor. *Liver Transpl* 2013;19(6):656-60.
81. Heath RL. Crisis preparation: planning for the inevitable. In: Millar DP, Heath RL, eds. *Responding to crisis: a rhetorical approach to crisis communication*. Mahwah NJ: Lawrence Erlbaum Associates; 2004.
82. U.S. Department of Health and Human Services. Centers for Disease Control and Prevention. *Crisis and emergency risk communication: Be first. Be right. Be credible*. CERC: Crisis Communication Plans [Internet], 2014, available at https://emergency.cdc.gov/cerc/ppt/CERC_Crisis_Communication_Plans.pdf, accessed 27 July 2021.
83. Institute for Public Relations. *Crisis management and communications* [Internet]. 2007, available at https://instituteforpr.org/crisis-management-and-communications/, accessed 27 July 2021.
84. Van der Laan J. Crisis Communication. In: Avsec D, Breidenbach T, Lingemann M, Logar Zakrajšek B, eds. *Communicating about organ donation and transplantation – A handbook on theoretical and practical aspects* [Internet]. Foedus Joint Action; 2016, pp. 139-48, available at www.trapianti.salute.gov.it/imgs/C_17_cntPagine_261_listaFile_itemName_0_file.pdf, accessed 27 July 2021.
85. Henderson ML, Hays R, Van Pilsum Rasmussen SE *et al.* Living donor program crisis management plans: current landscape and talking point recommendations. *Am J Transplant* 2020;20(2):546-52.
86. Conway J, Federico F, Stewart K, Campbell M. *Respectful management of serious clinical adverse events*. Cambridge MA: Institute for Healthcare Improvement (IHI); 2011, available at www.ihi.org/resources/Pages/IHIWhitePapers/RespectfulManagementSeriousClinicalAEsWhitePaper.aspx, accessed 27 July 2021.

Appendix 1. **Abbreviations and acronyms**

ABO	blood group according to the ABO system
ABRs	auditory brainstem responses in multimodal evoked potentials
ACLD	deaths with acute primary or secondary cerebral lesions
ADEM	acute disseminated encephalomyelitis
ADH	anti-diuretic hormone
ADM	aggressive donor management
ADPKD	autosomal dominant polycystic kidney disease
AE	adverse event
AFP	alpha fetoprotein and placental
AHA	American Heart Association
AJCC	American Joint Cancer Committee
ALCD	acute primary or secondary cerebral lesion
ALL	acute lymphoblastic leukaemia
ALT	alanine aminotransferase
anti-CMV	antibodies against *Cytomegalovirus* (total antibodies of IgG and IgM)
anti-EBV	antibodies against Epstein–Barr virus
anti-HBc	antibodies against the core antigen of the hepatitis B virus
anti-HBc-IgM	IgM-antibodies against the core antigen of the hepatitis B virus
anti-HBs	antibodies against the HBsAg-molecule of hepatitis B virus
anti-HCV	antibodies against hepatitis C virus
anti-HIV	antibodies against HIV
anti-HIV-1/2	antibodies against HIV subtypes 1 or 2
anti-HIV-1	antibodies against HIV subtype 1 only
anti-HIV-2	antibodies against HIV subtype 2 only
AOTDTA	Australian Organ and Tissue Donation and Transplantation Authority
APTT	activated partial thromboplastin test
AR	adverse reaction
ARE	adverse reaction and/or event
AST	American Society of Transplantation
AST	aspartate aminotransferase
ATP	adenosinetriphosphate
ATP	ancillary therapeutic product
AVP	arginine vasopressin
BAL	broncho-alveolar lavage
Banff	Banff classification of renal allograft pathology
BCG	bacillus Calmette–Guérin
BD	brain death
BDD	brain death diagnosis
BD/DNC	brain death or death by neurologic criteria
B-HCG	beta human chorionic gonadotropin
BilIN	biliary intraepithelial neoplasia
BKPyV	BK polyomavirus
BKV	BK virus
BM	bone marrow
BMI	body mass index
BNP	B-type natriuretic peptide
CA	cardiac arrest
CA	competent authority
CAD	coronary artery disease

CALM	contact–appoint–look ahead–make a decision [in dealing with strong reactions]
CB	cord blood
CBF	cerebral blood flow
CDC	Centers for Disease Control and Prevention (USA)
cDCD	controlled donation after circulatory death
CD-P-TO	Committee on Organ Transplantation of the Council of Europe
CEA	carcinoembryonic antigen
CEN	European Committee for Standardization
CET	Centre for Evidence in Transplantation
CETC	Certification of European Transplant Co-ordinators
CGH	comparative genomic hybridisation
CHIKV	chikungunya virus
CI	cardiac index
CIT	cold ischaemia time
CJD	Creutzfeld–Jakob disease
CKMB	creatine kinase muscle/brain isoenzyme
CML	chronic myeloid leukaemia
CMV	*Cytomegalovirus*
CNS	central nervous system
CNT	Centro Nazionale Trapianti (Italy)
CO	carbon monoxide
CO	cardiac output
Covid-19	Coronavirus disease 2019
CPAP	continuous positive airway pressure
CPK	creatinine phosphokinase
CPK-MB	creatinine phosphokinase-muscle/brain fraction
CPP	cerebral perfusion pressure
CPR	cardio-pulmonary resuscitation
CQI	continuous quality improvement
CRAB	carbapenem-resistant *Acinetobacter baumannii*
CRE	carbapenem-resistant *enterobacteriaceae*
CR-KP	carbapenem-resistant *Klebsiella pneumoniae*
CT	computed tomography
CTA	computed tomographic angiography (see §3.5.1.4)
CTC	circulating tumour cells
CTP	computed tomographic perfusion (see §3.5.1.6)
CVP	central venous pressure
D+/R–	donor has been infected by the pathogen, recipient is naïve (not infected)
D+/R+	both donor and recipient have been infected by the pathogen
D–/R+	donor is naïve (not infected), recipient has been infected by the pathogen
D–/R–	both donor and recipient are naïve (not infected by the pathogen)
DAA	direct-acting anti-viral agents
DBD	donation after brain death or after neurological determination of death
DBI	devastating brain injury
DC	donor co-ordinator
DCD	donation after circulatory determination of death
cDCD	controlled donation after circulatory death
uDCD	uncontrolled donation after circulatory death
DD	deceased donor
DDAVP®	[a trade name for] Desmopressin
DENV	dengue virus
DGF	delayed graft function
DI	diabetes insipidus
DIC	disseminated intravascular coagulation
DKG	Double Kidney Transplant Group
DNA	deoxyribonucleic acid
DNC	death determined by neurologic criteria
DO_2	oxygen delivery
DoC	Duty of Candour
DOD	deceased organ donation
DRI	donor risk index
DSO	Deutsche Stiftung Organtransplantation (Germany)
DTAC	Disease Transmission Advisory Committee (USA)
EBV	Epstein–Barr virus
ECD	expanded-criteria donor
ECDC	European Centre for Disease Prevention and Control
ECG	electrocardiogram
ECLS	extracorporeal life support
ECMO	extracorporeal circulation with membrane oxygenation
ED	emergency department
EDD	European Donation Day
EEA	European Economic Area
EEG	electroencephalogram (see §3.5.2.1)
EF	ejection fraction
EFQM	European Foundation for Quality Management
EG	ethylene glycol
eGFR	estimated glomerular filtration rate

ELISA	enzyme-linked immunosorbent assay
ELWI	extra-vascular lung water index
ENTV	elective non-therapeutic ventilation
EOL	end of life
EPAS	ET-pancreas allocation system
ERC	European Resuscitation Council
ESBL	extended-spectrum beta-lactamases
ESCIM	European Society of Intensive Care Medicine
ESGICH	ESCMID Study Group of Infection in Compromised Hosts
ESP	European Senior Program
ET	essential thrombocythemia
ET	Eurotransplant
$EtCO_2$	end-tidal carbon dioxide level
ETT	endotracheal tube
EU	European Union
EuSCAPE	EUropean Survey on CArbapenemase-Producing *Enterobacteriaceae*
FAP	familiar amyloid polyneuropathy
FDG	fluorodeoxyglucose
FFP	fresh frozen plasma
FiO_2	fraction of inspired oxygen
FISH	fluorescence *in situ* hybridisation
FMF	familial Mediterranean fever
FOUR	full outline of unresponsiveness (coma scale)
FP	framework programmes
FSME	[German term for] endemic viral tick-borne encephalitis
FWIT	functional warm ischaemic time
GBM	glioblastoma multiforme
GCS	Glasgow Coma Scale
G-CSF	granulocyte-colony stimulating factor
GDRI	geographical disease risk index
GFR	glomerular filtration rate
GGT	gamma-glutamyl transferase
GIST	gastro-intestinal stromal tumour
GLP	good laboratory practice
GMP	good manufacturing practice
GN	Gram negative
HAM	HTLV-associated myelopathy
HAV	hepatitis A virus
HBsAg	surface antigen of hepatitis B virus
HBV	hepatitis B virus
HCG	human chorionic gonadotropin
HCP	health care provider
HCV	hepatitis C virus
HDV	hepatitis D virus
HEA	hydroxyethylamidons
HELLP	syndrome of haemolysis, elevated liver enzymes, low platelets
HES	hydroxyethyl starch
HEV	hepatitis E virus
HHV8	human herpes virus-8
HIV	human immunodeficiency virus
HIV-1-p24-Ag	p24-antigen of HIV, subtype 1
HLA	human leukocyte antigen
HMP	hypothermic machine perfusion
HMPAO	hexamethylpropyleneaminoxime
^{99m}TcHMPAO	^{99m}Tc-labelled hexamethylpropyleneaminoxime [tracer used in scintigraphy]
HOTT	Combating trafficking in persons for the purpose of organ removal
HPA	hypothalamic-pituitary axis
HPC	haematopoietic progenitor cell
HPyVs	human polyomaviruses
HR	heart rate
HRP	hypothermic regional perfusion
HRT	hormonal replacement therapy
HSV	*Herpes simplex* virus
HTK	Histidine-tryptophan-ketoglutarate
HTLV1/2	human T-lymphotropic virus/human T-cell-leukaemia virus subtype 1/2
ICHS	intracerebral haemorrhage scale
ICOD	intensive care to facilitate organ donation
ICP	intracranial pressure
ICU	intensive care unit
ID-card	identification card
IGRA	interferon-gamma release assay
IHS	intracerebral haemorrhage scale
ILCOR	International Liaison Committee of Resuscitation
INR	international normalised ratio
IPITTR	Israel Penn International Transplant Tumor Registry
IRHCTT	International Registry on Hand and Composite Tissue Transplantation
IRI	ischaemia/reperfusion injury
ISHLT	International Society of Heart and Lung Transplantation
ISN	International Society for Nephrology
ISOL	intracranial space-occupying lesion
ISUP	International Society of Urological Pathology
ITBL	ischaemia-type biliary lesions
ITBVI	intra-thoracic blood volume index
IV	intravenous
IVC	inferior vena cava
IVS	intraventricular septum
IVSd	thickness of intraventricular septum in diastole
iVx	inactivated vaccine
JCAHO	Joint Commission on the Accreditation of Healthcare Organizations

JCI	Joint Commission International
JCPyV	JC polyomavirus
JPAC	Joint Professional Advisory Committee
KDIGO	*Kidney disease: improving global outcomes* [guidelines]
KDP	key donation person
KPD	kidney paired donation
KSHV	Kaposi sarcoma herpes virus
LCMV	lymphocytic choriomeningitis virus
LD	living donor
LDH	lactate dehydrogenase
LD-LR	living donor liver resection
LDLT	living donor liver transplantation
LDN	living donor nephrectomy
LH	left hepatectomy
LLH	left lateral hepatectomy
LOD	living organ donation
LTBI	latent tuberculosis infection
LV	left valve
LVEF	left ventricular ejection fraction
LVx	live vaccine
MAID	medical assistance in dying
MALORY	MALignancy in Organ donors and Recipient safetY
MAP	mean arterial pressure
MCL	medio-calvicular line
MDR	multidrug-resistant
MELD	model of end-stage liver disease
MERS-CoV	Middle East respiratory symptom coronavirus
MGUS	monoclonal gammopathies of undetermined significance
MI-LDN	minimally living donor nephrectomy
MPHO	medical products of human origin
MPN	myeloproliferative neoplasm
MRI	magnetic resonance imaging
MRSA	methillicine-resistant *Staphylococcus aureus*
MRT	magnetic resonance tomography
MSM	men who have sex with men
NAT	nucleic acid amplifying technique ('nucleic acid testing')
NEC	neuro-endocrine carcinoma
NET	neuro-endocrine tumour
NHMRC	National Health and Medical Research Council
NICU	neonatal intensive care unit
NIHSS	National Institute for Health Stroke Severity Scale
Notify	WHO Vigilance and Surveillance Database for MPHO
NR	non-reactive
NRP	normothermic regional perfusion
NSE	neuron-specific enolase
NTO	national transplant organisation
NURSE	naming–understanding–respecting–supporting–exploring [dealing with emotions]
OHES	out-of-hospital emergency services
OMF	osteomyelofibrosis
ONT	Organización Nacional de Trasplantes (Spain)
OPO	organ procurement organisation
OPTN	Organ Procurement and Transplantation Network (USA)
OTC	ornithine transcarbamylase
pa	pulmonary artery
$paCO_2$	pulmonary artery carbon dioxide
$PaCO_2$	partial pressure of carbon dioxide
PanIN	pancreatic intraepithelial neoplasia/lesions
paO_2	pulmonary artery oxygen
PaO_2	partial pressure of oxygen
PAOP	pulmonary arterial occlusion pressure
PASS	phaeochromocytoma of the adrenal gland: scaled score
PBC	primary biliary cirrhosis
PBPC	peripheral blood progenitor cells
PCC	phaeochromocytoma
PCR	polymerase chain reaction
pDBD	paediatric donation after the neurological determination of death
PDCA	plan–do–check–act cycle
pDCD	paediatric donation after the circulatory determination of death
PDSA	plan–do–study–act cycle
PEEP	positive end-expiratory pressure
PET	positron emission tomography
PGL	paraganglioma
PHS	public health service (USA)
PICU	paediatric intensive care unit
PLAP	placental alkaline phosphatase
PMF	primary myelofibrosis
PML	progressive multifocal leukoencephalopathy
PNF	primary non-function
PNF	permanent non-function
P-PASS	pre-procurement pancreas allocation: suitability score
PROMs	patient-reported outcome measures
PSA	prostate-specific antigen
PT	prothrombin time
pTis	tumour *in situ*
PTLD	post-transplant lymphoproliferative disorders
PV	polycythaemia vera

pvO_2	pulmonary vein blood-gas determination
QA	quality assurance
QAP	quality assurance programme
QC	quality criterion
QI	quality indicator
QIP	quality improvement programme
QMS	quality management system
QoL	quality of life
RCA	root cause analysis
RCC	renal cell carcinoma
RCT	randomised controlled trial
RH	right hepatectomy
RL	risk level
ROI	regions of interest (during measurement in studies of CTP)
RP	responsible person
SaBTO	Advisory Committee for the Safety of Blood, Tissues and Organs (UK)
SAE	serious adverse event
SaO_2	oxygen saturation
SAR	serious adverse reaction
SARE	serious adverse reaction and/or event
SARS-CoV-2	severe acute respiratory syndrome Coronavirus 2
SCD	standard criteria donor
SCS	static cold storage
SEPs	somatosensory evoked potentials in multimodal evoked potentials
SIRS	systemic inflammatory response syndrome
SMA	superior mesenteric artery
SoHO	substances of human origin
SOL	space-occupying lesion
SOP	standard operating procedure
SOT	solid-organ transplantation
SPECT	single-photon-emission computed tomography
SPIKES	setting–perception–invitation–knowledge–emotions–strategy/summary [breaking bad news]
SSRI	selective serotonin re-uptake inhibitor
STD	sexually transmitted disease
SVI	stroke volume index
SVR	systemic vascular resistance
SVRI	systemic vascular resistance index
TA-NRP	thoraco-abdominal NRP
TB	tuberculosis
TBE	tick-borne encephalitis
TC	transplant centre
TCA	tricyclic anti-depressant
TCD	transcranial Doppler
TPHA	*Treponema pallidum* haemagglutination
TPM	transplant procurement management
TSE	transmissible spongiform encephalopathies
TST	tuberculosis screening test
TTS	The Transplantation Society
uDCD	uncontrolled donation after circulatory death
UK	United Kingdom
UNOS	United Network for Organ Sharing (USA)
UTI	urinary tract infection
UW	University of Wisconsin
V&S	vigilance and surveillance
VCA	vascularised composite allograft
VZV	varicella–zoster virus
WHO	World Health Organization
WIT	warm ischaemia time
WLST	withdrawal of life-sustaining therapy
WNV	West Nile virus
X-ray	X radiation

Appendix 2. **Glossary**

Acirculatory time	See 'Primary warm ischaemia time'.
Actual organ donor	An actual organ donor is defined as a person (living or deceased) from whom at least one organ has been procured for transplant purposes.
Adverse event	An undesired and unexpected occurrence associated with any stage of the chain from donation to transplantation that might lead to harm in solid-organ transplant recipients or living organ donors. See also 'Serious adverse event'.
Adverse reaction	An unintended response, including a communicable disease, in the recipient or in the living donor that might be associated with any stage of the chain from donation to transplantation. See also 'Serious adverse reaction'.
Agonal phase	The period from withdrawal of ventilatory support until circulatory arrest.
Allocation	The process for the assignment and distribution of organs.
Ancillary tests	Auxiliary or supplementary tests used for the determination of death by neurologic criteria. Ancillary tests can assess electro-physiological activity or brain blood flow.
Apnoea test	Procedure to evaluate the cessation of the spontaneous breathing reflex regulated by the respiratory centres located in the brainstem.
Asystolic time	See 'Primary warm ischaemia time'.
Audit	Periodic, independent, documented examination and verification of activities, records, processes and other elements of a quality system to determine their conformity with specific internal or external requirements. Audits may be conducted by professional peers, internal quality system auditors or auditors from certification bodies.
Banff classification	Schema for nomenclature and classification of renal allograft pathology, established in 1991 by Kim Solez and Lorraine Racusen in Banff, Canada. This classification has become the main instrument for setting standards in renal transplant pathology and is widely used in international clinical trials of new anti-rejection agents.
Brain death	Death determined by neurologic criteria on the basis of evidence of irreversible loss of neurological functions, in persons with acute primary or secondary devastating cerebral lesions, induced by intracranial events or the result of extracranial phenomena, such as hypoxia.
Cell	The smallest transplantable and functional unit of life.
Circulatory death	Death determined by circulatory criteria based on evidence of irreversible or permanent loss of the circulatory function.
Clinical triggers	Specific medical criteria that, when met, should result in referral of the possible deceased organ donor to the donor co-ordinator or the staff of the corresponding organ procurement organisation by the treating physician.
Cold ischaemia time	The elapsed time between the cooling of an organ after its blood supply has been cut off and the time when the organ is reperfused by circulation in the recipient. This interval can occur while the organ is still in the body or after it is removed from the body, and applies only to organs stored by static cold storage. In cases of machine perfusion, it is not appropriate to use the term without providing more detailed information on the conditions (solutions, temperatures, oxygenation etc.) applied.

Compensation Reimbursement strictly limited to making good the expenses and inconvenience related to the donation.

Competent Authority See 'Health Authority'.

Consent to donation/ authorisation of donation Legally valid permission from a person to donate an organ. In cases of living donation, this person must be given appropriate information beforehand about the purpose and nature of the intervention as well as its consequences and risks.

Consented eligible organ donor An eligible organ donor with consent given in whom an operative incision has been made with the intention of organ procurement for the purpose of transplantation.

Controlled donation after circulatory death Donation from a person whose death has been established by circulatory criteria, following an expected circulatory arrest.

D+/R– Combination of a seropositive donor and a seronegative recipient for a given infectious disease. This combination should raise questions about the prophylactic measures to be taken to protect the recipient from harm.

D+/R+ When both the donor and the recipient have been infected by a given pathogen.

D–/R+ Combination of a seronegative donor and a seropositive recipient for a given infectious disease.

D–/R– When both the donor and recipient are naïve for (i.e. have not been infected by) a given pathogen.

Delayed graft function Manifestation of acute graft injury, with attributes unique to the transplant process, in which the graft takes up function with some delay after implantation. See also 'Intermediate graft function'.

Devastating brain injury Neurological injury where there is an immediate threat to life from a neurologic cause and where limitation of therapy is being considered in favour of palliative and end-of-life care.

Diabetes insipidus Form of diabetes caused by a deficiency of the pituitary hormone vasopressin, which restricts the rate of water excretion in the kidney. Clinical triggers for identification of this complication in deceased organ donors, related to the failure of the hypothalamic-pituitary axis, are polyuria (in the case of appropriate volume therapy) and hypernatraemia.

Distribution The process of transport and delivery of organs after they have been allocated.

Donation after brain death Donation from a person who has been declared dead on the basis of the irreversible loss of neurological functions.

Donation after circulatory death Donation from a person who has been declared dead on the basis of circulatory criteria. Depending on the clinical scenario in which cardiac arrest occurs, it can be classified as controlled or uncontrolled and in one of the four Maastricht categories. See also 'Controlled donation after circulatory death' and 'Uncontrolled donation after circulatory death'.

Donor A person, living or deceased, who is a source of one or several organs.

Donor assessment and selection The process of determining the suitability of a potential donor, living or deceased, to donate. This process allows a prediction of whether the transplantation of one or several of their organs will be safe for the recipient(s).

Donor card Personal document stating agreement to organ donation.

Donor characterisation The process of collecting the relevant information on the characteristics of the donor needed to evaluate their suitability for organ donation, in order to undertake a proper risk assessment, minimise the risks for the recipient and optimise organ allocation.

Donor co-ordinator Person responsible for the proactive identification of potential donors at hospital level and for co-ordination and support of all the subsequent steps supporting organ donation, including organ procurement and distribution. They may also be called 'transplant co-ordinator', 'key donation person' or other names.

Donor risk index Scoring system describing organ quality in a population from whom this score has been derived by multivariable statistical methods.

Elective non-therapeutic ventilation The initiation of mechanical ventilation, in patients with a devastating brain injury in whom further treatment is deemed futile, with the aim of incorporating the option of organ donation into their end-of-life care.

Eligible organ donor A person who has been found medically suitable to become an organ donor.

Expanded-criteria donor A donor in whom co-morbidities exist that may compromise organ function. This concept should not be confused with the non-standard-risk donor, for which see 'Non-standard-criteria donor'.

Export The process of transporting human organs, tissues or cells intended for human application to another country where they are to be processed further or used.

Failed donor A possible donor who did not become an actual donor.

False negative A test result which improperly indicates absence of a condition (the result is negative) when in reality the condition is present. An example of a false negative would be if a test designed to detect a given infection returned a negative result but the person actually did have the infection. Some common causes of a 'false negative' result include haemodilution, window period, investigation of the incorrect body compartment or inappropriate test quality.

False positive A test result which improperly indicates presence of a condition (the result is positive) when in reality the condition is absent. An example of a false positive would be if a test designed to detect a given infection returned a positive result but the person actually did not have the infection. Some common causes of a 'false positive' include contamination, cross-reactivity or inappropriate test quality.

Follow-up Subsequent evaluation of the health of a patient, living donor or recipient, for the purposes of monitoring the results of the donation or transplantation, maintenance of care and initiation of post-donation or post-transplant interventions. See also 'Surveillance' (which is part of 'Follow-up').

Functional warm ischaemia time The period between the first episode of significant hypoperfusion and the start of *in situ* preservation.

Good practice A method or technique that has consistently shown results superior to those achieved by other means and which is currently used as a benchmark.

Graft Part of the human body that is transplanted in the same person or another person to replace a damaged part or to compensate for a defect.

Haemodilution Dilution of serum or blood sample used for laboratory investigations, due to infusions and transfusions.

Health Authority In the context of this Guide, a national or regional body to which the government has delegated the responsibility for ensuring that organ donation and transplantation are appropriately promoted, regulated and monitored in the interests of patient safety and public transparency. The terms Regulatory Authority, Regulatory Agency or, in the EU, Competent Authority are equivalent to it.

Implantation See 'Transplantation'.

Import The process of transporting human organs, tissues or cells into one country from another for the purpose of further processing or use.

Imputability Assessment of the probability that a reaction in a living donor or a recipient may be attributed to the process of donation or transplantation, or to an aspect of the safety or quality of the transplanted organ, tissue or cell.

Informed consent A person's voluntary agreement, based upon adequate knowledge and understanding of relevant information, to donate an organ or to undergo a diagnostic, therapeutic or preventive procedure.

Intensive care to facilitate organ donation The initiation or continuation of intensive care measures in patients with a devastating brain injury, in whom further treatment is deemed futile, with the aim of incorporating the option of organ donation into their end-of-life care.

Intermediate graft function The terms 'slow graft function' and 'intermediate graft function' are used in liver transplantation as equivalent to delayed graft function in kidney transplantation for the delayed start of graft function after transplantation. See also 'Delayed graft function'.

Ischaemia time The period during which an organ is deprived of its blood supply. See 'Cold ischaemia time' and 'Warm ischaemia time'. See also 'Functional warm ischaemia time', 'Lukewarm ischaemia time', 'Primary warm ischaemia time' and 'Total ischaemia time'.

Labelling The process, including the steps taken to identify the packaged material, of attaching all appropriate information to a container or package so that the information is clearly visible on the exterior of the carton, receptacle or packaging.

Living donor A living person from whom organs, tissues or cells have been removed for the purpose of transplantation. A living donor has one of these possible relationships with the recipient:

A. Related
A1. Genetically-related:
First-degree genetic relative: parent, sibling, offspring.
Second-degree genetic relative: grandparent, grandchild, aunt, uncle, niece, nephew.
Other than first or second degree genetically related, e.g. cousin.
A2. Emotionally related:
Spouse (if not genetically related), in-law, adopted, friend.

B. Unrelated = Non-related
Not genetically or emotionally related.

Lukewarm ischaemia time The uncontrolled period between the events of stopping of organ perfusion and proper storage of the graft in cold storage or on machine perfusion.

Lung-protective treatment	Strategy applied in potential organ donors with the goal of increasing the number of lungs eligible for transplant. It includes these methods to prevent atelectasis and infection: continuous mucolysis, humidification of respiratory gases, aspiration of secretions, changes of body position and head-of-bed elevation (if no contraindications).
Model for end-stage liver disease	Scoring system for predicting survival in end-stage liver disease based on laboratory data for bilirubin, creatinine and international normalised ratio.
Negative	Any 'negative' test result indicates only that the pathogen has not been detected. The medical community documents this as 'negative' without knowing whether the pathogen was missed or whether it did not exist. Equivalent to 'non-reactive'.
Next of kin	A person's closest living relative(s).
Non-reactive	See 'Negative'.
Non-resident donor or recipient	A person donating an organ or receiving a transplant who does not reside permanently in the country where donation or transplantation takes place.
Non-standard-criteria donor	Donor in whom evidence of disease-transmission risk exists. The risk can be graded according to risk levels (which differ for infectious diseases and malignancies). This concept should not be confused with the 'expanded-criteria donor' concept.
Normothermic regional perfusion	*In situ* perfusion of organs with oxygenated blood using a device applied at normothermic temperatures.
Notify	WHO Vigilance and Surveillance Database for medical products of human origin.
Operating procedure	See 'Procedure'.
Opting-in donation system	A system where consent to donation has to be given explicitly from the donor or the next of kin. Also called 'explicit consent' or 'informed consent' system.
Opting-out donation system	A system where donation can take place if there is no objection registered to donation. In practice, operational variations exist, just as with the 'opting-in' system in Europe, because the family still plays a prominent role in the decision-making process. Also (inappropriately) called 'presumed consent' system.
Organ	A differentiated part of the human body, formed by different tissues, that maintains its structure, vascularisation and capacity to develop physiological functions with a significant level of autonomy. A part of an organ is also considered to be an organ if its function is to be used for the same purpose as the entire organ in the human body, maintaining the requirements of structure and vascularisation.
Organ characterisation	The process of collecting the relevant information on the characteristics of the organ, needed to evaluate its suitability, in order to undertake a proper risk assessment, to minimise the risks for the recipient and to optimise organ allocation.
Organ procurement organisation	A healthcare establishment, a person, a team or unit of a hospital, or any other body which undertakes or co-ordinates the procurement of organs and is authorised to do so by the responsible Health Authority under the regulatory framework in the member state concerned.
Positive	Any 'reactive' test result that indicates either current or past exposure to a pathogen, after exclusion of a false positive result. Equivalent to 'reactive'.
Possible organ donor	A patient with a devastating brain injury or lesion or a patient with a circulatory failure who is apparently medically suitable for organ donation.
Potential organ donor	A potential DBD (donation after brain death) donor is a person whose clinical condition is suspected to fulfil brain-death criteria. A potential DCD (donation after circulatory death) donor is either a person whose circulatory and respiratory functions have ceased, and cardio-pulmonary resuscitation measures are not to be attempted or continued, or a person in whom the cessation of circulatory and respiratory functions is anticipated to occur within a time frame that will enable organ recovery.
Pre-emptive transplantation	In renal transplantation this term is used for cases where transplant is performed prior to the start of dialysis as renal replacement therapy.
Preservation	The use of chemical agents, alterations in environmental conditions or other means during processing to prevent or inhibit biological or physical deterioration of organs between procurement and transplantation.
Presumed consent	See 'Opting-out donation system'.
Primary non-function	The situation when a graft never functions following transplantation.
Primary warm ischaemia time	Primary WIT (asystolic or acirculatory time) is the period between circulatory arrest and the start of *in situ* preservation.
Procedure	Description of the operation(s) or process(es) to be carried out, the precautions to be taken and measures to be applied that relate directly and indirectly to the transplant process from donation to transplantation.
Procurement	The removal of organs, tissues or cells from a donor for the purpose of transplantation. The terms 'recovery' and 'retrieval' are equivalent to it.

Protocol	A combination of a standard operating procedure and standard documentation.
Quality assurance	Describes the actions planned and performed to provide confidence that all systems and elements that influence the quality of the product are working as expected, individually and collectively.
Quality control	Part of quality management, focused on fulfilling quality requirements.
Quality criteria	Conditions that have to be met by the healthcare practice in order to be considered a good-quality practice.
Quality improvement	Describes the actions planned and performed to develop a system to review and improve the quality of a product or process.
Quality indicator	A defined measurement that indicates the presence and intensity of a phenomenon or event.
Quality management	A system that monitors and coordinates activities in an organisation to ensure consistent quality in care, safety and use of resources. This general term encompasses everything that can affect the final quality of organs, tissues and cells.
Quality system	The organisational structure, defined responsibilities, procedures, processes and resources for implementing quality management, including all the activities that contribute to quality (directly or indirectly).
Reactive	See 'Positive'.
Recipient	A person who receives transplanted organs, tissues and/or cells.
Recovery	See 'Procurement'.
Registry	A repository of data collected on organ donors and/or transplant recipients for the purpose of outcome assessment, quality assurance, healthcare organisation, research and surveillance.
Risk assessment	Identification of potential hazards, with an estimate of the likelihood that they will cause harm and of the severity of the harm if it does occur.
Self-assessment	A comprehensive and systematic review of the organisation's activities and results, referenced against the quality management system or a model of excellence, which can help identify areas requiring improvement.
Serious adverse event	Any undesired and unexpected occurrence associated with any stage of the chain from donation to transplantation that might lead to the transmission of a communicable disease, to death or life-threatening, disabling or incapacitating conditions for patients or that results in, or prolongs, hospitalisation or morbidity.
Serious adverse reaction	An unintended response – including a communicable disease in the living donor or in the recipient, and which might be associated with any stage of the chain from donation to transplantation – that is fatal, life-threatening, disabling or incapacitating, or which results in (or prolongs) hospitalisation or morbidity.
Slow graft function	The terms 'slow graft function' and 'intermediate graft function (IGF)' are used in liver transplantation as equivalent to delayed graft function in kidney transplantation for the delayed start of graft function after transplantation.
Standard-criteria donor	A donor manifesting no evidence of disease-transmission risk and no co-morbidities compromising organ function.
Strout test	Concentration test for the diagnosis of acute Chagas disease. This test has a sensitivity of 80-90 % and is recommended in the case of patients strongly suspected of having acute Chagas disease and returning negative results for the direct fresh-blood exam.
Surveillance	The systematic ongoing collection, collation and analysis of data for public health purposes, and the timely dissemination of public health information for assessment and public health response, as necessary. See also 'Follow-up' (which includes surveillance).
Tissue	An aggregate of cells joined together by, for example, connective structures and performing a particular function.
Total ischaemia time	The time from cessation of adequate circulation to an organ (cross-clamping) in a donor until arterial reperfusion in the recipient. During this period, multiple organ-preservation technologies can be applied.
Traceability	Ability to locate and identify an organ at each stage in the chain from donation to transplantation/disposal, including the ability to identify the donor, the donor hospital and the recipient(s) at the transplant centre(s), and to locate and identify all relevant non-personal information relating to products and materials coming into contact with that organ.
Transmissible disease	Any clinically evident illness (i.e. with characteristic medical signs and/or symptoms of disease) that results from – or could result from – the infection, presence and growth of micro-organisms in an individual recipient, having originated from the organs, tissues or cells applied.
Transplantation/ implantation/ grafting	Surgical procedure in which an organ (or organs) from a donor is (are) inserted into a recipient with the aim of restoring function(s) in the body.

Transplant centre	A healthcare establishment which undertakes the transplantation of organs and is authorised to do so by the Health Authority under the national regulatory framework.
Uncontrolled donation after circulatory death	Donation from persons whose death has been established by circulatory criteria, following an unexpected circulatory arrest.
Utilised organ donor	An actual donor from whom at least one organ has been transplanted.
Vigilance	Alertness to or awareness of adverse events, adverse reactions or complications related to the donation and clinical application of human organs, tissues and cells, involving an established process for reporting at local, regional, national or international level.
Warm ischaemia time (WIT)	The time an organ remains at body temperature after its blood supply has been reduced or cut off but before it is cooled or reconnected to a blood supply.
Warm ischaemia time: international usage	Netherlands: WIT means primary WIT. UK: WIT means functional WIT. US: WIT means time from withdrawal of life support in donor to *in situ* preservation.
Warm ischaemia time in controlled DCD	In cDCD, total WIT extends from the moment when ventilatory support is withdrawn until the start of *in situ* preservation (with cold preservation fluid or abdominal regional perfusion). It includes the agonal phase, primary WIT and functional WIT.
Warm ischaemia time in uncontrolled DCD	In uDCD, total WIT extends from the moment the donor suffers the sudden and unexpected cardiac arrest until the start of *in situ* preservation (with cold preservation fluid or abdominal regional perfusion).
Window period	The time between potential exposure to an infectious pathogen and the point when the test will give an accurate result. During the window period a person can be infected with the pathogen and transmit it to others but have a negative or non-reactive test result.

Appendix 3. Criteria for the identification of potential donors after brain death in a retrospective clinical chart review (Spain)

The Spanish quality assurance programme for the deceased donation process has established criteria to identify potential donation after brain death (DBD) donors during a retrospective clinical chart review.* By using these criteria, professionals performing potential donor audits can classify patients in one of five categories of potential DBD donor – confirmed, highly probable, possible, not assessable or not potential – in a consistent and reproducible manner. A conservative assessment of the potential donor pool would take into account only the 'confirmed' or 'highly probable' DBD donor cases. A less conservative approach would also take into account the 'possible' DBD donor cases.

Situation 1: confirmed potential DBD donor

To consider a patient as a confirmed potential DBD donor, any of the following circumstances must be present:

- All legal requirements to confirm brain death have been properly reflected in the clinical chart.
- A neurologist or a neurosurgeon has examined the patient and has recorded that brain death has occurred, and there is no evidence against this diagnosis.
- An intensive care physician has recorded that brain death has occurred, and there is no evidence against this diagnosis.

Situation 2: highly probable potential DBD donor

A patient is considered a highly probable potential DBD donor in the following circumstances:

- aetiology + conditions + 1 finding (at least) in clinical examination + 1 clinical sign (at least); or
- aetiology + conditions + 2 findings (at least) in clinical examination.

For more detail, see Table A3.1.

Situation 3: possible potential DBD donor

A patient is considered a possible potential DBD donor in the following circumstances:

- aetiology + conditions + 1 finding (at least) in clinical examination; or
- aetiology + conditions + 1 clinical sign (at least).

For more detail, see Table A3.1.

Situation 4: not assessable as a potential DBD donor

A patient is not assessable as a potential DBD donor in any of the following circumstances:

- The aetiology of the process is known, severe and consistent with brain death, but there is no

* De la Rosa G, Domínguez-Gil B, Matesanz R *et al.* Continuously evaluating performance in deceased donation: the Spanish Quality Assurance Program. *Am J Transplant* 2012;12(9):2507-13 (https://doi.org.10.1111/j.1600-6143.2012.04138.x).

additional information in the clinical chart or the clinical chart is not available.

- The aetiology of the process is known, is severe and can lead to brain death, but the diagnosis could not be confirmed because life-sustaining therapies were withdrawn.
- The aetiology of the process is known, is severe and can lead to brain death, but the patient was exposed to barbiturates or neuromuscular blocking drugs at the moment of cardiac arrest.
- Infratentorial processes with no legal diagnosis of brain death.

Situation 5: not considered as a potential DBD donor

In circumstances other than those described above, the patient will not be considered a potential DBD donor.

Table A3.1. **Issues to be considered, based on the available information in the clinical chart, when defining a person as being a highly probable or a possible potential donor after brain death**

Aetiology of the process causing death
It must be one of the known aetiologies of brain death and must be severe enough to cause brain death.
Conditions
Absence or no evidence of spontaneous breathing and movements.
Findings in clinical examination
• Progressing non-reactive mydriasis, i.e. *de novo* non-reactive mydriasis in a patient with a severe neurological condition, in the context of a severe clinical deterioration and which is not explained by drug interference. • Absence of at least one of the following brainstem reflexes: corneal, oculocephalic, oculovestibular, cough and gag. • Negative atropine test.
Clinical signs
• Abrupt arterial hypotension, other causes apart from brain death having been discarded. • Abrupt polyuria, other causes apart from brain death having been discarded. • Refractory and progressive intracranial hypertension (intracranial hypertension which has evolved in the minutes or hours prior to death, towards limits that provoke a cerebral perfusion pressure of 0 or close to 0 mmHg, with no response to therapy).

Appendix 4. **Synopsis of national codes for neurological determination of death in infants and children in 10 European countries**

Modified from Petry A; Lücking KM; Krüger M (unpublished data)

Austria

Österreichisches Bundesinstitut für Gesundheitswesen (ÖBIG), Oberster Sanitätsrat: Empfehlungen zur Durchführung der Hirntoddiagnostik bei einer geplanten Organentnahme (2013)*

Concept of cessation of brain function	yes
Concept of cessation of brain stem function	no
Concept of cessation of cardiocirculatory function	yes
Doctors (number)	2
Paediatrician mandatorily involved	no, but experienced specialists (neurologists, neurosurgeons, intensive care physicians)
Preconditions	irreversible loss of function of the cerebrum, the cerebellum and the brain stem; presence of acute primary or secondary brain damage
Exclusion of	presence of acute primary or secondary brain damage
Measurement of drug level	only for high dose barbiturates (alternative: detection of cerebral circulatory arrest)
Known aetiology	yes
Core temperature	≥ 34 °C
Clinical examination without ancillary tests	yes, for primary supratentorial cause (if EEG or detection CCA not possible) with age-dependent observation period
Coma	yes (GCS 3)
Apnoea	yes
Absence of brain stem reflexes	yes
Pupillary response to light	yes
Oculocephalic reflex	yes
Vestibulo-ocular reflex	yes
Corneal reflex	yes
Motor response to pain in the distribution of cranial nerve V	yes
Motor response to pain outside the distribution of cranial nerve V	yes
Gag reflex	yes
Tracheal reflex	yes
Jaw jerk	yes
Ciliospinal reflex	yes
Oculocardial reflex	not defined

* https://transplant.goeg.at/sites/transplant.goeg.at/files/2017-06/Empfehlungen%20zur%20Durchf%C3%BChrung%20der%20Hirntoddiagnostik%20bei%20einer%20geplanten%20Organentnahme%20inkl.%20Protokoll.pdf.

Austria

Sucking reflex	not defined
Flaccid tetraplegia	yes
Atropine test	yes
Others	no
Number of clinical tests	2
Preterms	not defined
Age limit to diagnose brain death	7 days
Newborn	7 days until 2 months
Newborn particularities	2nd clinical examination after 72 h, if EEG or proof of CCA not possible; sole clinical examination only in case of primary supratentorial damage
Infant	2 months to 2 years
Infant particularities	2nd clinical examination after 72 h, if EEG or proof of CCA not possible; sole clinical examination only in case of primary supratentorial damage
Toddlers	> 2 years
Toddler particularities	primary supratentorial: 2nd exam after 12 h or AT secondary: mandatory AT primary infratentorial: mandatory AT 2nd clinical examination in all cases
Limit on use of same criteria as for adults	2 years
Differentiation of primary and secondary brain damage	yes
Differentiation of infratentorial and supratentorial brain damage	yes
Ancillary tests	[not specified]
Cerebral blood flow	yes
EEG	yes
EP	no
Ancillary tests to shorten or replace observation period	yes, cannot replace second clinical examination

Belgium

Unités multidisciplinaires (2007): Transplantation (Centre) Diagnostic de mort encéphalique (2007)*	
Concept of cessation of brain function	yes
Concept of cessation of brain stem function	no
Concept of cessation of cardiocirculatory function	yes
Doctors (number)	3
Paediatrician mandatorily involved	doctors of the ICU; or, if not available: neurologist who has done EEG or neuro-surgeon who has looked after patients
Preconditions	irreversible damage of the entire brain (hemispheres and brainstem)
Exclusion of	toxic cause of coma (hypnotics, sedatives, alcohol, drugs), endocrine cause, metabolic cause or secondary cause (hypothermia < 32 °C)
Measurement of drug level	not defined
Known aetiology	yes
Core temperature	≥ 32 °C
Clinical examination without ancillary tests	yes, whenever conditions and age are fulfilled: 6 h after start of coma and apnoea
Coma	yes
Apnoea	yes
Absence of brain stem reflexes	yes
Pupillary response to light	yes
Oculocephalic reflex	yes
Vestibulo-ocular reflex	yes
Corneal reflex	yes
Motor response to pain in the distribution of cranial nerve V	no
Motor response to pain outside the distribution of cranial nerve V	no
Gag reflex	yes
Tracheal reflex	yes
Jaw jerk	no
Ciliospinal reflex	no
Oculocardial reflex	yes or atropine test
Sucking reflex	no
Flaccid tetraplegia	no

* http://www.erasme.ulb.ac.be/.

Belgium

Atropine test	not defined
Others	yes or oculocardial reflex
Number of clinical tests	1 (adults and children older than 1 year of age)
Preterms	not defined
Age limit to diagnose brain death	not defined
Newborn	<2 months
Newborn particularities	2nd examination after 48 h observation period
Infant	2 months to 1 year
Infant particularities	2 clinical examinations with observation period of 24 h
Toddlers	> 1 year
Toddler particularities	one clinical examination 6 h after beginning of unconsciousness and apnoea
Limit on use of same criteria as for adults	1 year
Differentiation of primary and secondary brain damage	no
Differentiation of infratentorial and supratentorial brain damage	no
Ancillary tests	
Cerebral blood flow	yes
EEG	yes
EP	yes
Ancillary tests to shorten or replace observation period	not defined

Denmark

Sundhedsstyrelsen, Dansk Neurokirurgisk Selskabs „Hjernedødsudvalg" Konstatering af Hjernedød (2013)*	
Concept of cessation of brain function	yes
Concept of cessation of brain stem function	no
Concept of cessation of cardiocirculatory function	yes
Doctors (number)	2
Paediatrician mandatorily involved	the treating physician, plus another physician who must be (mandatory): specialist in neurology, neurosurgery or clinical neurophysiology
Preconditions	unconsciousness, lack of reaction, apnoea; brain damage not treatable and leads to death; unconsciousness and loss of spontaneous breathing for at least 6 h; blood pressure > = 90 mmHg; pupils medium or rigid
Exclusion of	other causes of unconsciousness and absence of reaction: intoxication with alcohol, sedatives, narcotics, muscle relaxants, sedatives, antiepileptic drugs; all diseases that can cause unconsciousness or changes in blood count must be corrected
Measurement of drug level	not defined
Known aetiology	yes
Core temperature	≥ 35 °C
Clinical examination without ancillary tests	yes, if preconditions given and other causes of coma excluded: two clinical examinations with an interval of at least one hour
Coma	yes
Apnoea	yes
Absence of brain stem reflexes	yes
Pupillary response to light	yes
Oculocephalic reflex	yes
Vestibulo-ocular reflex	yes
Corneal reflex	yes
Motor response to pain in the distribution of cranial nerve V	yes
Motor response to pain outside the distribution of cranial nerve V	yes
Gag reflex	yes
Tracheal reflex	yes
Jaw jerk	no
Ciliospinal reflex	no
Oculocardial reflex	no

* http://www.tilogaard.dk/Hjernedoedsundersoegelse_december_2013.pdf.

Denmark

Sucking reflex	no
Flaccid tetraplegia	no
Atropine test	no
Others	no
Number of clinical tests	2
Preterms	not defined
Age limit to diagnose brain death	1 year
Newborn	not defined
Newborn particularities	not defined
Infant	< 1 year
Infant particularities	guideline: mandatory ancillary test (law: no brain death diagnostic possible because no reliable criteria)
Toddlers	> 1 year
Toddler particularities	2 clinical examinations with observation period of 1 h
Limit on use of same criteria as for adults	1 year
Differentiation of primary and secondary brain damage	yes
Differentiation of infratentorial and supratentorial brain damage	yes
Ancillary tests	
Cerebral blood flow	yes
EEG	no
EP	no
Ancillary tests to shorten or replace observation period	no

France

Agence de la biomédecine : Recommandations formalisées d'experts sur la prise en charge des patients en vue d'un prélèvement d'organes (donneurs en état de mort encéphalique et à cœur arrêté)(2019)*

Concept of cessation of brain function	yes
Concept of cessation of brain stem function	no
Concept of cessation of cardiocirculatory function	no (procedure in progress)
Doctors (number)	2
Paediatrician mandatorily involved	no, but experienced specialists in PICU and NICU (intensive care physicians)
Preconditions	irreversible destruction of the whole brain function (hemispheres and brain stem)
Exclusion of	intoxication, clinical examination influenced by drugs, blood pressure ≥ appropriate for age, unstable metabolic and endocrinal disorders
Measurement of drug level	mainly for barbiturates
Known aetiology	yes
Core temperature	≥ 35 °C
Clinical examination without ancillary tests	clinical examination supported by TCD
Coma	yes (GCS 3)
Apnoea	yes
Absence of brain stem reflexes	yes
Pupillary response to light	yes
Oculocephalic reflex	yes
Vestibulo-ocular reflex	yes
Corneal reflex	yes
Motor response to pain in the distribution of cranial nerve V	yes
Motor response to pain outside the distribution of cranial nerve V	yes
Gag reflex	yes
Tracheal reflex	yes
Jaw jerk	no
Ciliospinal reflex	yes
Oculocardial reflex	yes
Sucking reflex	yes
Flaccid tetraplegia	no

* https://www.agence-biomedecine.fr/Recommandations-formalisees-d-experts-sur-le-prelevement-et-la-greffe.

France

Atropine test	no (but alternative to oculocardial reflex)
Others	no
Number of clinical tests	2
Preterms	not defined
Age limit to diagnose brain death	≥ 37 WGA
Newborn	0-28 days
Newborn particularities	2 clinical examinations by 2 doctors, and highly recommended CCA on TCD monitoring, mandatory AT (angio > EEG)
Infant	29-365 days
Infant particularities	2 clinical examinations by 2 doctors, and highly recommended CCA on TCD monitoring, mandatory AT (EEG or angio)
Toddlers	> 1 year
Toddler particularities	2 clinical examinations by 2 doctors, and highly recommended CCA on TCD monitoring, mandatory AT (EEG or angio)
Limit on use of same criteria as for adults	no
Differentiation of primary and secondary brain damage	no
Differentiation of infratentorial and supratentorial brain damage	no
Ancillary tests	
Cerebral blood flow	yes
EEG	yes (2 EEG with 4 h interval, and more caution below 1 month)
EP	no
Ancillary tests to shorten or replace observation period	no

Germany

Bundesärztekammer: Richtlinie gemäß §16 Abs. 1 S. 1 Nr. 1 TPG für die Regeln zur Feststellung des Todes nach §3 Abs. 1 S. 1 Nr. 2 TPG und die Verfahrensregeln zur Feststellung des endgültigen, nicht behebbaren Ausfalls der Gesamtfunktion des Großhirns, des Kleinhirns und des Hirnstamms nach §3 Abs. 2 Nr. 2 TPG, Vierte Fortschreibung (2015)*

Concept of cessation of brain function	yes
Concept of cessation of brain stem function	no
Concept of cessation of cardiocirculatory function	no
Doctors (number)	2
Paediatrician mandatorily involved	yes, mandatory for death before 1 year of age, recommended in deaths from 2 to 14 years of age
Preconditions	acute severe primary or secondary brain damage
Exclusion of	intoxication, damping drugs, neuromuscular blockage, reversible brainstem or peripheral nervous system disorders, circulatory shock, coma in endocrine, metabolic or inflammatory disease
Measurement of drug level	yes, for newborns and infants (especially when anticonvulsivants, sedative, analgesics)
Known aetiology	yes
Core temperature	≥ 35 °C
Clinical examination without ancillary tests	yes, for primary supratentorial or secondary cause of brain damage from beginning of 2nd year of life
Coma	yes
Apnoea	yes
Absence of brain stem reflexes	yes
Pupillary response to light	yes
Oculocephalic reflex	yes
Vestibulo-ocular reflex	yes
Corneal reflex	yes
Motor response to pain in the distribution of cranial nerve V	yes
Motor response to pain outside the distribution of cranial nerve V	yes
Gag reflex	yes
Tracheal reflex	yes
Jaw jerk	no
Ciliospinal reflex	no
Oculocardial reflex	not defined

* http://www.bundesaerztekammer.de/fileadmin/user_upload/downloads/irrev.Hirnfunktionsausfall.pdf.

Germany

Sucking reflex	not defined
Flaccid tetraplegia	no
Atropine test	yes
Others	no
Number of clinical tests	2
Preterms	<37 WGA not applicable
Age limit to diagnose brain death	≥ 37 WGA
Newborn	0-28 days
Newborn particularities	2nd clinical examination after 72 h, mandatory ancillary test
Infant	29-730 days
Infant particularities	2nd clinical examination after 24 h, mandatory ancillary test
Toddlers	> 730 days
Toddler particularities	primary supratentorial: 2nd exam after 12 h or AT secondary: 2nd exam after 72 h or AT primary infratentorial: mandatory AT
Limit on use of same criteria as for adults	1 year
Differentiation of primary and secondary brain damage	yes
Differentiation of infratentorial and supratentorial brain damage	yes
Ancillary tests	
Cerebral blood flow	yes
EEG	yes
EP	BAEP yes; others not less than 2 years of age
Ancillary tests to shorten or replace observation period	yes, can replace second clinical examination when age > 2 years

Hungary

Magyar Közlöny: A Kormány tagjainak rendeletei: Az emberi erőforrások minisztere 12/2012. (VIII. EMMI rendelete az egészségügyről szóló 1997. évi CLIV. törvénynek a szerv- és szövetátültetésre, valamint -tárolásra és egyes kórszövettani vizsgálatokra vonatkozó rendelkezései végrehajtásáról szóló 18/1998. (XII. 27.) EüM rendelet módosításáról (2012)*

Concept of cessation of brain function	yes
Concept of cessation of brain stem function	no
Concept of cessation of cardiocirculatory function	not defined
Doctors (number)	3
Paediatrician mandatorily involved	not defined
Preconditions	not defined
Exclusion of	intoxication and drug overdose; neuromuscular blockade shock; metabolic or endocrinological coma; fulminant inflammatory brain disease
Measurement of drug level	not defined
Known aetiology	yes
Core temperature	≥ 35 °C
Clinical examination without ancillary tests	yes, with observation period
Coma	yes
Apnoea	yes
Absence of brain stem reflexes	yes
Pupillary response to light	yes
Oculocephalic reflex	no
Vestibulo-ocular reflex	yes
Corneal reflex	yes
Motor response to pain in the distribution of cranial nerve V	yes
Motor response to pain outside the distribution of cranial nerve V	no
Gag reflex	yes
Tracheal reflex	yes
Jaw jerk	no
Ciliospinal reflex	no
Oculocardial reflex	no
Sucking reflex	no

* http://www.ovsz.hu/sites/ovsz.hu/files/szervadomanyozas_dokumentum/csatolmanyok/tajekoztato_rendelet_modositasrol/18-1998-rendelet-modosito.pdf.

Hungary

Flaccid tetraplegia	no
Atropine test	no
Others	not defined
Number of clinical tests	not defined
Preterms	not defined
Age limit to diagnose brain death	0 days
Newborn	0 days until 5 weeks
Newborn particularities	observation period 72 h
Infant	5 weeks to 3 years
Infant particularities	observation period 24 h
Toddlers	> 3 year
Toddler particularities	primary brain damage: 12 h; secondary brain damage: 72 h
Limit on use of same criteria as for adults	3 years
Differentiation of primary and secondary brain damage	yes
Differentiation of infratentorial and supratentorial brain damage	no?
Ancillary tests	
Cerebral blood flow	yes
EEG	no
EP	no
Ancillary tests to shorten or replace observation period	yes

Poland

***Monitor Polski, Dziennik Urzędowy Rzeczypospolitej Polskiej*, Warszawa, dnia 17 stycznia 2020 r., Poz. 73, Obwieszczenie Ministra Zdrowia z dnia 4 grudnia 2019 r. w sprawie sposobu i kryteriów stwierdzenia trwałego nieodwracalnego ustania czynności mózgu** (2020)*

Concept of cessation of brain function	yes
Concept of cessation of brain stem function	no
Concept of cessation of cardiocirculatory function	yes, separate act, established in 2010
Doctors (number)	2
Paediatrician mandatorily involved	no, but two doctors must be involved: first, a neonatologist or anaesthesiologist; second, a neurosurgeon, neurologist or paediatric neurologist
Preconditions	catastrophic brain injury, brain stem areflexia, absence of confounders
Exclusion of	exclusion of intoxication, metabolic disturbances, hypothermia <35 °C, hypotension – MAP within age limits
Measurement of drug level	yes, but may be ignored in cases of elapsed elimination time or positive brain blood perfusion test
Known aetiology	yes
Core temperature	≥ 35 °C
Clinical examination without ancillary tests	yes, with exception of the presence of confounders or infratentorial brain damage
Coma	yes
Apnoea	yes
Absence of brain stem reflexes	yes
Pupillary response to light	yes
Oculocephalic reflex	yes
Vestibulo-ocular reflex	yes
Corneal reflex	yes
Motor response to pain in the distribution of cranial nerve V	yes
Motor response to pain outside the distribution of cranial nerve V	no
Gag reflex	yes
Tracheal reflex	yes
Jaw jerk	no
Ciliospinal reflex	no
Oculocardial reflex	no

* https://isap.sejm.gov.pl/isap.nsf/DocDetails.xsp?id=WMP20200000073.

Poland

Sucking reflex	no
Flaccid tetraplegia	no
Atropine test	no
Others	not defined
Number of clinical tests	2
Preterms	WGA< 37 not applicable
Age limit to diagnose brain death	>37 WGA and >48 h after birth
Newborn	0-28 days
Newborn particularities	primary observation time between onset of brain stem areflexia and first examination >48 h, 2nd examination after next >24 h
Infant	> 28 days of age, infants and toddlers without differences, as one uniform group
Infant particularities	not defined
Toddlers	> 28 days
Toddler particularities	1st examination after > 24 h; 2nd examination after next 24 h
Limit on use of same criteria as for adults	> 28 days, observation time and time distance between two series of clinical tests are longer
Differentiation of primary and secondary brain damage	yes
Differentiation of infratentorial and supratentorial brain damage	yes
Ancillary tests	
Cerebral blood flow	yes
EEG	yes
EP	yes
Ancillary tests to shorten or replace observation period	yes, may shorten observation period to 3 h in children > 28 days

Spain

Ministerio de Sanidad, Servicios Sociales e Igualdad: Boletín oficial del Estado Real Decreto 1723/2012, de 28 de diciembre, por el que se regulan las actividades de obtención, utilización clínica y coordinación territorial de los órganos humanos destinados al trasplante y se establecen requisitos de calidad y seguridad. BOE Núm. 313 (2012)*

Concept of cessation of brain function	yes
Concept of cessation of brain stem function	no
Concept of cessation of cardiocirculatory function	yes
Doctors (number)	3
Paediatrician mandatorily involved	no, but it is obligatory to have a neurologist or neurosurgeon and the head of the department or his/her representative
Preconditions	irreversible loss of brain function
Exclusion of	haemodynamic instability; inadequate oxygenation and respiration; metabolic and endocrine changes that can cause coma; metabolic and endocrinological changes; sedative substances and pharmaceuticals that can cause coma; neuro-muscular inhibitors
Measurement of drug level	extended observation period
Known aetiology	yes
Core temperature	≥ 33 °C in adults, ≥ 36 °C in children up to 24 months
Clinical examination without ancillary tests	yes, almost always: observation time 6 h for known structural lesion; 24 h for anoxic encephalopathy
Coma	yes
Apnoea	yes
Absence of brain stem reflexes	yes
Pupillary response to light	yes
Oculocephalic reflex	yes
Vestibulo-ocular reflex	yes
Corneal reflex	yes
Motor response to pain in the distribution of cranial nerve V	yes
Motor response to pain outside the distribution of cranial nerve V	yes
Gag reflex	yes
Tracheal reflex	yes
Jaw jerk	no
Ciliospinal reflex	no
Oculocardial reflex	no

* https://www.boe.es/diario_boe/txt.php?id=BOE-A-2012-15715.

Spain

Sucking reflex	yes (newborns and infants)
Flaccid tetraplegia	no
Atropine test	yes
Others	rooting reflex
Number of clinical tests	2 or more (newborns and preterms)
Preterms	<37 WGA possible although no accepted international guidelines; observation period of 48 h, period can be shortened by ancillary tests
Age limit to diagnose brain death	no
Newborn	>37 WGA until 30 days
Newborn particularities	observation period of 24 h
Infant	>30 days to 24 months
Infant particularities	observation period of 12 h
Toddlers	> 2 years
Toddler particularities	observation period 6 h in cases of known structural lesion, 24 h in anoxic encephalopathy
Limit on use of same criteria as for adults	2 years
Differentiation of primary and secondary brain damage	yes
Differentiation of infratentorial and supratentorial brain damage	yes
Ancillary tests	
Cerebral blood flow	yes
EEG	yes
EP	yes
Ancillary tests to shorten or replace observation period	yes

Switzerland

Schweizerische Akademie der Medizinischen Wissenschaften (SAMW): Feststellung des Todes mit Bezug auf Organtransplantationen Medizin-ethische Richtlinien (2011)*

Concept of cessation of brain function	yes
Concept of cessation of brain stem function	no
Concept of cessation of cardiocirculatory function	yes
Doctors (number)	2
Paediatrician mandatorily involved	continuing education in paediatric intensive care or neuro-paediatrics
Preconditions	irreversible loss of function of the brain including the brain stem
Exclusion of	metabolic cause of coma relaxation; suspected brain infection or polyradiculitis cranialis; sign of any drug or toxic cause
Measurement of drug level	not defined
Known aetiology	yes
Core temperature	≥ 35 °C
Clinical examination without ancillary tests	yes >1 year of life (2 clinical examinations at the same time), infants: 2 clinical examinations with observation interval of 24 h
Coma	yes
Apnoea	yes
Absence of brain stem reflexes	yes
Pupillary response to light	yes
Oculocephalic reflex	yes
Vestibulo-ocular reflex	yes
Corneal reflex	yes
Motor response to pain in the distribution of cranial nerve V	yes
Motor response to pain outside the distribution of cranial nerve V	yes
Gag reflex	yes
Tracheal reflex	yes
Jaw jerk	no
Ciliospinal reflex	no
Oculocardial reflex	not defined
Sucking reflex	not defined
Flaccid tetraplegia	no

* https://www.samw.ch/dam/jcr:9f60a9e3-b52a-4584-aa10-3dbd39c6d9e5/richtlinien_samw_tod_organtransplantation.pdf.

Switzerland

Atropine test	yes
Others	no
Number of clinical tests	2
Preterms	not defined
Age limit to diagnose brain death	> 28 days
Newborn	0-28 days (44 with postm.)
Newborn particularities	no organ donation because of ethical and medical reasons
Infant	29-365 days
Infant particularities	2nd clinical examination after 24 h
Toddlers	> 1 year
Toddler particularities	four-eyes principle (clinical examinations at the same time)
Limit on use of same criteria as for adults	1 year
Differentiation of primary and secondary brain damage	yes
Differentiation of infratentorial and supratentorial brain damage	no
Ancillary tests	
Cerebral blood flow	yes
EEG	no
EP	no
Ancillary tests to shorten or replace observation period	not defined

United Kingdom

Academy of Medical Royal Colleges: A code of practice for the diagnosis and confirmation of death (2008)*

RCPCH: Diagnosis of death by neurological criteria (DNC) in infants less than two months old – clinical guideline (2015)†

Concept of cessation of brain function	no
Concept of cessation of brain stem function	yes
Concept of cessation of cardiocirculatory function	yes
Doctors (number)	2
Paediatrician mandatorily involved	two paediatricians, registered for more than five years and competent in the procedure, and at least one of them should be a consultant
Preconditions	irreversible cessation of brain stem function
Exclusion of	intoxication, sedative drugs, neuromuscular blocking agents, severe electrolyte, acid-base or endocrine abnormality
Measurement of drug level	yes
Known aetiology	yes
Core temperature	≥ 35 °C
Clinical examination without ancillary tests	yes
Coma	yes
Apnoea	yes
Absence of brain stem reflexes	yes
Pupillary response to light	yes
Oculocephalic reflex	no
Vestibulo-ocular reflex	yes
Corneal reflex	yes
Motor response to pain in the distribution of cranial nerve V	yes
Motor response to pain outside the distribution of cranial nerve V	no
Gag reflex	yes
Tracheal reflex	yes
Jaw jerk	no
Ciliospinal reflex	no
Oculocardial reflex	no

* https://www.aomrc.org.uk/reports-guidance/ukdec-reports-and-guidance/code-practice-diagnosis-confirmation-death/.

† https://www.rcpch.ac.uk/resources/diagnosis-death-neurological-criteria-dnc-infants-less-two-months-old-clinical-guideline/.

United Kingdom

Sucking reflex	no
Flaccid tetraplegia	no
Atropine test	no
Others	no
Number of clinical tests	2
Preterms	<37 WGA not possible because development of brain stem reflexes of preterms not well known, reflex paths not completely myelinated
Age limit to diagnose brain death	≥ 37 WGA
Newborn	>37 WGA until 2 months
Newborn particularities	in post-asphyxiated infants, or those receiving intensive care after resuscitation: period of at least 24 h of observation before clinical testing
Infant	not defined
Infant particularities	not defined
Toddlers	> 2 months
Toddler particularities	2 clinical examinations with no observation period between them; only short observation interval before for normalisation of blood gases and other parameters
Limit on use of same criteria as for adults	2 months
Differentiation of primary and secondary brain damage	no
Differentiation of infratentorial and supratentorial brain damage	no
Ancillary tests	
Cerebral blood flow	yes
EEG	yes
EP	yes
Ancillary tests to shorten or replace observation period	no

Appendix 5. Procurement surgery in brain-death donors: tasks for the anaesthesiologist

This appendix gives information on the management of procurement surgery by the anaesthesiologist in the operating room (theatre), with specific goals and strategies to optimise the outcome for the organ recipient.

General

1. Donor management will be continued until organ preservation (see Chapter 5).
2. Often volume depletion will be underestimated at the intensive care unit (ICU) prior to procurement surgery: volume resuscitation until urine output > 1 mL/kg/h, mean arterial pressure (MAP) > 60 mmHg, central venous pressure (CVP) 4-8 mmHg, SvO_2 > 70 %, lactate < 2 mmol/L.
3. If diabetes insipidus continues to persist: antidiuretic hormone (ADH) substitution, correct Na^+ (< 155 mmol/L). Avoid hypokalaemia (may result in ventricular fibrillation, e.g. by electrocoagulation): K^+ 3.5-4.5 mmol/L). Try to achieve a blood glucose < 180 mg/dL.
4. If the donor is haemodynamically unstable: during preparation of the large retroperitoneal vessels, alteration in blood pressure occurs (e.g., vena cava compression due to manipulation of the vessels), which may be corrected by short-acting agents. Thereby the effect of intervention is seen with delay, and inverse events may occur because the cause of lack of venous return does not exist any more (e.g. no longer vena cava compression). In cases of arterial hypertension, the MAP usually drops by itself. After tapering catecholamines, sevoflurane may be used because of its controllable side-effect of vasodilation and its short action. Haemodynamic instability may be exacerbated by hypovolaemia (before and during procurement). Hypotension with hypoperfusion impact on long-term organ function is higher than when using vasopressors.
5. Spinal reflexes exist in brain-death donors. They occur during positioning on the table, incision of abdominal walls (skin nerves) and retroperitoneal preparation (e.g. plexus solaris). They should be blocked by muscle-relaxing agents (as well as opiates to block the spinal receptors). During further surgery such spinal vegetative reactions may induce tachycardia up to 120 bpm, flushing and sweating when preparing area of plexus solaris and/or adrenal glands.
6. Avoid uncontrolled hypothermia.
7. Continue lung-protective ventilation (to achieve PaO_2 > 100 mmHg, O_2-saturation > 98 %, PEEP ≥ 8 cmH_2O). In cases of lung procurement, the lung team will suggest adjustment of ventilation. If no lung procurement, ensure proper oxygenation and ventilation of other organs without further consideration of long-term lung damage.

Preparation prior to surgery in intensive care unit

1. All relevant documents should go to the operating room (cross-check with co-ordinator).

2. Transfusions are usually not needed (if Hb > 7 g/dL). The only exception might be heart preservation with normothermic machine perfusion when appropriate erythrocyte function is needed for priming the system (check with co-ordinator and heart team): then Hb should be at 10.0 g/dL. In case of untraceable bleeding (e.g. rupture of vertebral artery) you may need multiple units without prior crossmatch and may want to switch to cDCD/uDCD technology.
3. Actual monitoring data, blood gas analysis (BGA), coagulation, electrolytes and haemoglobin.
4. All syringe pumps and/or infusion pumps are continued during transport and in the operating room (with backup for 3 h).
5. For transport to the operating room: prepare according to standards of transfer for any ICU patient (consider transport and emergency equipment); many hospitals apply muscle relaxants before departure from ICU (spinal reflexes, see General point 5 above). During transport, spinal-vegetative reflexes may occur (MAP goes up).
6. Pre-operative antibiotics according to indication at hospital standards, if requested at all. Selective decontamination of the intestine is not necessary unless requested. Acid-blocking agents are no longer required. Continue thrombosis prophylaxis.
7. Check for special medications with co-ordinator and teams (e.g. 250-500 mg bolus methylprednisolone).

Preparation prior to surgery in operating room

1. See advice above, and use standard emergency equipment for a patient haemodynamically unstable with severe systemic pro-inflammatory response (SIRS). Prepare Heparin 25 000 IU.
2. Ensure access available to draw blood samples for BGA etc., convenient monitoring including diuresis. For positioning: ask surgeons.
3. Before skin incision: team timeout.
4. For organ preservation, have available two infusion poles: 10-15 L physiologic sterile flush solution (e.g. 0.9 % NaCl), check whether defibrillator and/or sterile paddles are available in case of a heart procurement. During organ preservation, the scrub nurse will need enough suction equipment to collect about 20 L within a few minutes.
5. Avoid heat loss until organ preservation.

Special issues per organ

Basic surgery: Recycle knowledge from the modules of hemicolectomy with retroperitoneal inspection, Whipple surgery, sternotomy, lung surgery until organ preservation.

Pancreas: Depending on surgical strategy, pancreas with duodenal segment will be mobilised prior to organ preservation (inclusive gastrectomy). Prior to stapling, some centres prefer to decontaminate the duodenum with 300-500 mL of diluted povidone–iodine and they will ask to remove the gastric tube. Controversy exists about indication of further intestinal decontamination. During mobilisation of the pancreas, vasoactive mediators will be delivered, causing severe fluctuation of MAP.

Liver: In stable donors, *in situ* splitting may be considered (consider basic knowledge of hemihepatectomy).

Heart: During opening of the pericardium and marking of the large vessels, depression of the circulation may occur with arrhythmia (especially in case of volume depletion and electrolyte disorders).

Lung: Bronchoscopy by lung team ($FiO_2 = 1$, multiple BGA, equipment provided by lung team). Lung team may perform recruitment under visual and manual protection of the lung against barotrauma. Then adjust ventilation according to instruction of the lung surgeon. Optionally, BGA from the lung veins may be helpful to check whether a single lung can be used or whether lung segments may be resected at the recipient hospital if indicated. Continue ventilation during organ preservation according to the instructions of the lung surgeon.

Intestine: Pre-procurement briefing necessary with responsible surgeon.

For every organ: Blood specimen must be drawn before organ preservation (ask co-ordinator).

After dissection of all organs and vessels

The following steps (depending on kind of procurement) occur after dissection of all organs and vessels. Heparinisation (20 000-30 000 IU IV, or 300 IU/kg IV) prior to cannulation (of abdominal aorta for preservation of all abdominal organs, of ascending aorta for the heart, of pulmonary artery for lung). Some teams apply prostacyclin (100-200 µg IV) before crossclamp (please be aware of immediate vasodilation: blood pressure drops irreversibly within a few seconds). Prior to crossclamp, the heart team will/should ask for removal of central venous catheter. After crossclamp, lung ventilation should be continued in accordance with lung surgeon's advice. In case of normothermic heart preservation, 1 000 mL of blood may be drawn from aorta with an acceptable hypotension of < 30 secs. Please note that,

for all these steps, instructions have to be given by the procurement teams.

Then crossclamp of aorta and opening of vena cava/ left ear of heart and start of flush by organ. The use of the preservation solution is done according to manufacturer's guidance by the procurement teams. All anaesthesiologic interventions are stopped except for continued lung ventilation. Here the lung surgeon will ask for targeted ventilation manoeuvres prior to stapling of trachea upon removal of the lung from the thoracic cavity. During organ preservation with vascular flushout by preservation solution, topical cooling will be applied by a sludge prepared from 4 °C cold solution by the procurement team. After the flush the procurement teams must perform final dissection of each organ, which will leave the body in this sequence:

a. heart,
b. lung,
c. intestine,
d. liver,
e. pancreas,
f. kidney,
g. spleen or lymphnodes for compatibility testing,
h. vessel tool kits (arteriovenous *iliaca communis*, aortic arch) for reconstruction.

Surgery is done when the wound has been closed. After organ preservation and during final dissection of all organs, all venous and arterial lines as well as other indwelling material must be removed with the aim that proper post-procurement respect is possible for donor relatives. (Only exception: coroner or state attorney explicitly requests hospital not to remove any line).

Suggested further reading

Anderson TA, Bekker P, Vagefi PA. Anesthetic considerations in organ procurement surgery: a narrative review. *Can J Anaesth* 2015 May; 62(5):529-39.

Appendix 6. **Checklist for the anaesthesiologist in the operating room**

Specific goals and strategies to optimise the outcome for the organ recipient

General			
1. Volume resuscitation until:			
• urine output > 1 mL/kg/h	☐ yes	☐ no	☐ n/a
• MAP > 60 mmHg	☐ yes	☐ no	☐ n/a
• CVP 4-8 mmHg	☐ yes	☐ no	☐ n/a
2. Diabetes insipidus persists?			
• ADH substitution	☐ yes	☐ no	☐ n/a
• correct Na^+ (< 155 mmol/L)	☐ yes	☐ no	☐ n/a
• correct K^+ to 3.5-4.5 mmol/L)	☐ yes	☐ no	☐ n/a
• achieve a blood glucose < 180 mg/dL	☐ yes	☐ no	☐ n/a
3. Haemodynamically unstable?			
• need to use short-acting agents to increase MAP?	☐ yes	☐ no	☐ n/a
• need to use sevoflurane in case of arterial hypertension?	☐ yes	☐ no	☐ n/a
4. Are spinal reflexes present during procedure?			
• need to use muscle-relaxing agents?	☐ yes	☐ no	☐ n/a
• need to use opiates to block the spinal receptors?	☐ yes	☐ no	☐ n/a
• need to control spinal vegetative reactions?	☐ yes	☐ no	☐ n/a
5. Uncontrolled hypothermia avoided?	☐ yes	☐ no	☐ n/a
6. Lung-protective ventilation with PEEP ≥ 8 cmH_2O (to achieve PaO_2 > 100 mmHg, SpO_2 > 98 %)	☐ yes	☐ no	☐ n/a
or adjusted according to the lung team (only for lung procurement)	☐ yes	☐ no	☐ n/a

Preparation at the intensive care unit prior to surgery			
7. Transfusions needed (Hb < 7g/dL)? **or**	☐ yes	☐ no	☐ n/a
• > 10 g/dL (exception for heart preservation with normothermic machine perfusion)	☐ yes	☐ no	☐ n/a
8. Chart with updated data:			
• monitoring	☐ yes	☐ no	☐ n/a
• blood-gas analysis (BGA)	☐ yes	☐ no	☐ n/a
• coagulation	☐ yes	☐ no	☐ n/a
• electrolytes	☐ yes	☐ no	☐ n/a
• haemoglobin	☐ yes	☐ no	☐ n/a
9. All syringe and/or infusion pumps are maintained and have backup battery for 3 hours	☐ yes	☐ no	☐ n/a
10. For transport to the operating room:			
• standard precautions as for critically ill patient (including emergency equipment)	☐ yes	☐ no	☐ n/a
• donor paralysed before departure from ICU	☐ yes	☐ no	☐ n/a
11. Preoperative antibiotics administered?	☐ yes	☐ no	☐ n/a
12. Thrombosis prophylaxis continued?	☐ yes	☐ no	☐ n/a
13. Need of special medications confirmed with co-ordinator and teams (e.g. 250-500 mg bolus methylprednisolone)	☐ yes	☐ no	☐ n/a

Note: ADH anti-diuretic hormone; CVP central venous pressure; ICU intensive care unit; MAP mean arterial pressure; n/a not applicable; OR operating room.

Preparation prior to surgery in the operating room			
14. Adequate monitoring including arterial line, urinary output; for positioning, ask surgeons	❑ yes	❑ no	❑ n/a
15. Avoid heat loss until organ preservation	❑ yes	❑ no	❑ n/a
16. Prepare Heparin 25 000 IU	❑ yes	❑ no	❑ n/a
17. For organ preservation, have available two infusion poles and 10-15 L of adequate sterile solution (4 °C)	❑ yes	❑ no	❑ n/a
18. During organ preservation, prepare suction equipment to collect about 20 L within a few minutes	❑ yes	❑ no	❑ n/a
19. Check that defibrillator and/or sterile paddles are available in case of heart procurement	❑ yes	❑ no	❑ n/a
20. Before skin incision: team timeout	❑ yes	❑ no	❑ n/a
21. Prepare to draw blood specimen before organ preservation (ask co-ordinator for which organs)	❑ yes	❑ no	❑ n/a

Special issues			
Follow instructions given by the procurement team depending on kind of procurement	❑ yes	❑ no	❑ n/a
Stop all anaesthesiology interventions when lung ventilation is no longer indicated	❑ yes	❑ no	❑ n/a
Sequence of organ procurement is: heart, lung, intestine, liver, pancreas, kidney, spleen or lymph nodes	❑ yes	❑ no	❑ n/a
Surgery is done when the wound has been closed	❑ yes	❑ no	❑ n/a
For proper post-procurement protocol/respect by donor relatives:			
Remove all venous and arterial lines as well as other indwelling material. (Only exception: coroner or state attorney explicitly requests hospital not to remove any line.)	❑ yes	❑ no	❑ n/a

Note: ADH anti-diuretic hormone; CVP central venous pressure; ICU intensive care unit; MAP mean arterial pressure; n/a not applicable; OR operating room.

Appendix 7. The use of steroids in the management of deceased donors

Summary of findings

Although retrospective studies, including some large registry studies, have shown improved organ donation rates and transplant outcomes with donor steroid treatment, there is no evidence from randomised controlled trials (RCTs) across heart, lung, liver and kidney transplantation that donor treatment with steroids improves organ donation/transplant rates or transplant outcomes. The difference between the RCTs and cohort studies may lie in the incomplete correction for confounding factors in retrospective studies. Another reason for the discrepancy could be the small size of most RCTs so far conducted, which may be underpowered for small potential differences in outcomes such as: number of organs retrieved and graft survival. However, the most recently published RCT in renal transplantation was adequately powered and showed no significant difference in DGF, acute rejection or graft survival.

Clinical question

'Does the intravenous administration of steroids to potential deceased organ donors improve transplant rates and/or transplant outcomes?'

PICOS

Population: Adult patients over the age of 18 admitted to an ICU with the diagnosis of death by neurological criteria as a potential organ donor.

Intervention: Intravenous administration of steroids in the ICU, including methylprednisolone or hydrocortisone at any dose (e.g. 15 mg/kg of methylprednisolone or 100 mg in bolus plus 200 mg/24h of hydrocortisone).

Comparator: Placebo-controlled, standard of care, no therapy, and different therapy. Treatment comparisons of interest will include methylprednisolone therapy in monotherapy and/or combination therapy regimens against each other or against an alternative control group.

Outcomes: The primary outcome will be the number of organs transplanted by donor. The secondary outcomes will be early organ function (heart, lung, liver and kidney).

Study Design: Systematic reviews, with or without meta-analysis to be included and randomised controlled trials.

Search strategy and results

The Transplant Library (TL) was searched from inception to 26 May 2020. The TL includes all randomised controlled trials and systematic reviews in the field of solid organ transplantation published as full text or in abstract form, sourced from MEDLINE, EMBASE and the Cochrane Library.

The search strategy used is as follows:

1. Steroid.mp. or exp Steroids/
2. Prednisolone.mp. or exp Prednisolone/
3. Exp Methylprednisolone Acetate/ or Methylprednisolone.mp. or exp Methylprednisolone or exp Methylprednisolone Hemisuccinate
4. Hydrocortisone.mp.or exp Hydrocortisone/
5. Predn$.m_titl.
6. Corti$.m_titl

7. Hormon$.m_titl.
8. Hydrocort$.m_titl.
9. Methylpred$.m_titl.
10. Donor.ab. or donor.titl.
11. Donation.ab or donation.titl.
12. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9
13. 10 or 11
14. 12 and 13

Searches identified 202 potentially relevant references; from these, 15 references were selected for full text review. One additional study was identified from review references. Nineteen references met the inclusion criteria defined above. Of these, 4 were systematic reviews, and 15 reported outcomes from 9 randomised controlled trials.

Systematic reviews

Turco *et al.* (2019). Hormone replacement therapy in brain-dead organ donors: a comprehensive review with an emphasis on traumatic brain injury. *The Journal of Trauma and Acute Care Surgery* 86(4): 702-9.

This review included 15 cohort studies, focussing on donors with traumatic brain injury. The authors included all hormone replacement therapy with varying combinations of thyroid hormone, insulin and corticosteroids. The review is narrative and does not include any meta-analysis; 14 of the included studies demonstrated an increased organ procurement rate with hormone replacement therapy, although the effects of each hormone type in isolation are difficult to extract. It should be noted that this review appears to miss a number of the RCTs identified below and the risks of bias and confounding are only discussed in general.

D'Aragon *et al.* (2017). Effect of corticosteroid administration on neurologically deceased organ donors and transplant recipients: a systematic review and meta-analysis. *BMJ Open*. 7(6): e014436.

This well-conducted systematic review included 11 RCTs; 8 studies used methylprednisolone administration in the study arm *versus* usual care or placebo, while 3 used either methylprednisolone or hydrocortisone in combination with liothyronin, *versus* placebo. A single dose of methylprednisolone intravenously was the most common regimen, ranging in dose from 1 g to 5 g. No individual trial reported results suggesting increased organ recovery rates with steroids. One study reported reduced transaminase levels following liver transplantation within 10 days where the donor had received steroids (Kotsch: see below), but another, similar sized study found similar transaminase levels (Amatschek: see below). Meta-analysis is presented in this systematic review for a composite graft dysfunction outcome combining: creatinine level, creatinine clearance, dialysis, listing for kidney transplant or death at different time intervals, using 6 studies in renal transplantation and 2 studies in liver transplantation, showing no significant effect of corticosteroids.

Dupuis *et al.* (2014). Corticosteroids in the management of brain-dead potential organ donors: a systematic review. *British Journal of Anaesthesia*. 113(3): 346-59.

This is a well-conducted systematic review including 11 RCTs (as in D'Aragon *et al.* 2017, above) but also including 14 observational studies; 10 of the 14 observational studies reported organ recovery rates, 9 finding an improvement in the number of organs retrieved when using corticosteroids. Overall quality of included studies was poor and with a high risk of confounding due to retrospective cohorts and concomitant use of other hormone therapy, such as thyroid hormones or vasopressin.

Rech *et al.* (2013). Management of the brain-dead organ donor: a systematic review and meta-analysis. *Transplantation* 95(7): 966-74.

This systematic review looks at various aspects of donor management, including the use of steroids. The authors included 20 RCTs in total and 6 of these RCTs analysed the effect of steroids (alongside thyroid hormones in 2). The authors concluded that the use of methylprednisolone did not increase lung procurement rates, nor improve renal function after kidney transplantation. No meta-analysis was performed for the effect of steroids on transplant outcomes.

Randomised controlled trials

Reindl-Schwaighofer *et al.* (2019). Steroid pretreatment of organ donors does not impact on early rejection and long-term kidney allograft survival: Results from a multicenter randomized, controlled trial. *American Journal of Transplantation*. 19(6): 1770-76.

Wilflingseder *et al.* (2010). Impaired metabolism in donor kidney grafts after steroid pretreatment. *Transplant International*. 23(8): 796-804.

Kainz *et al.* (2010). Steroid pretreatment of organ donors to prevent postischemic renal allograft failure:

a randomized, controlled trial. *Annals of Internal Medicine*. 153(4): 222-30.

The long-term outcomes from this good quality, multicentre RCT in renal transplantation have been published since the reviews discussed above and are therefore not included in any of those reviews. A total of 455 renal transplant recipients received kidneys from donors randomised to receive 1 g methylprednisolone or placebo; a blinded study drug was provided to be administered. The study was powered for significant changes in delayed graft function and 5-year graft survival. There were extremely low numbers of kidneys not transplanted in both arms of the study. There was no significant difference seen in delayed graft function, nor biopsy-proven acute rejection. At 5 years after transplantation there was no significant difference in graft survival and no difference in estimated GFR; 5-year follow up was available for 97 % of randomised patients.

Jafari *et al.* (2018). Down-regulation of inflammatory signaling pathways despite up-regulation of Toll-like receptors; the effects of corticosteroid therapy in brain-dead kidney donors, a double-blind, randomized, controlled trial. *Molecular Immunology*. 94: 36-44.

This is a small RCT comparing 2 different regimens of methylprednisolone for brain dead donors with live donor renal transplantation. The paper concentrates on serum markers of inflammation rather than clinical outcomes. The first treatment group had increased levels of pro-inflammatory cytokines such as IL-1, IL-6 and TNF-alpha. As these levels were lower in the second treatment arm (which received more methylprednisolone) the authors have concluded that treatment with non-standard methylprednisolone reduces inflammation close to the level seen in live donors, but standard treatment increases the immunogenicity of organs prior to retrieval. Serum creatinine of recipients is presented to 6 months after transplant, showing a significantly higher creatinine in those whose donor received 15 mg/kg/day of methylprednisolone, but similar levels between kidneys from live donors and brain-dead donors who received additional methylprednisolone.

Amatschek *et al.* (2012). The effect of steroid pretreatment of deceased organ donors on liver allograft function: a blinded randomized placebo controlled trial. *Journal of Hepatology*. 56(6): 1305-9.

This is a good quality, multicentre RCT in liver transplantation whereby 90 donors were randomised to receive 1 g methylprednisolone or placebo. There was no significant difference in 3-year recipient survival or biopsy-proven acute rejection, but the study was not powered for these outcomes; it was designed to assess the serum trajectory of liver transaminases as a surrogate for ischaemia-reperfusion injury, also finding no significant difference in this outcome.

Venkateswaran *et al.* (2009). The haemodynamic effects of adjunctive hormone therapy in potential heart donors: a prospective randomized double-blind factorially designed controlled trial. *European Heart Journal* 30(14): 1771-80.

Venkateswaran *et al.* (2009). The proinflammatory environment in potential heart and lung donors: prevalence and impact of donor management and hormonal therapy. *Transplantation* 88(4): 582-8.

Venkateswaran *et al.* (2008). Early donor management increases the retrieval rate of lungs for transplantation. *Annals of Thoracic Surgery* 85(1): 278-86.

Venkateswaran *et al.* (2010). Echocardiography in the potential heart donor. *Transplantation* 89(7): 894-901.

James *et al.* (2010). The effects of acute triiodothyronine therapy on myocardial gene expression in brain stem dead cardiac donors. *Journal of Clinical Endocrinology & Metabolism* 95(3): 1338-43.

This RCT in potential lung and heart donors compares combinations of methylprednisolone, triiodothyronine, both drugs or placebo. The study was of good quality and included 80 potential cardiac donors and 120 potential lung donors. The early management of potential lung donors in the trial arm included several interventions that are not part of standard care and a post hoc analysis was done to assess the outcomes of donors receiving steroids. Methylprednisolone was not associated with increased donation rate of lungs, nor lung transplant outcomes. Methylprednisolone did not impact cardiac index of potential cardiac donors, cardiac transplant rate, nor outcomes of cardiac transplant. Use of hormone replacement had no effect on biomarkers of inflammation.

Kotsch *et al.* (2008). Methylprednisolone therapy in deceased donors reduces inflammation in the donor liver and improves outcome after liver transplantation: a prospective randomized controlled trial. *Annals of Surgery* 248(6): 1042-50.

This is a well-conducted RCT in liver transplantation whereby donors were randomised to placebo or 250 mg methylprednisolone bolus followed by 100 mg/h infusion. The study was powered to detect a 50 % difference in serum AST on day 1 after transplantation. The study found that both

AST and ALT were significantly reduced for the first 10 days for livers from donors receiving steroid pretreatment, and that treated livers had a reduced risk of biopsy-proven acute rejection in the first 6 months (protocol biopsies). There were no significant differences in INR, lactate or serum albumin during the first 10 days and there is no information about procurement rates or graft loss.

Mariot *et al.* (1991). Evaluation of tri-iodothyronine and cortisol treatment in the brain-dead patient. *Annales Francaises d'Anesthesie et de Reanimation* 10(4): 321-8.

This double-blind study randomised 40 potential donors to receive either T3 and cortisone or placebo. The authors found no difference in haemodynamic stability, metabolic profile or suitability for transplantation between groups.

Soulillou *et al.* (1979). Steroid-cyclophosphamide pretreatment of kidney allograft donors. A control study. *Nephron*. 24:193-7

This is a small RCT (34 recipients) of renal transplants; deceased donors were randomised to 5 g methylprednisolone + 5 g cyclophosphamide compared to saline placebo infusion. Patients and outcome assessors were blinded to the treatment allocation. There was no significant difference in renal function or graft survival up to 12 months.

Jeffery *et al.* (1978). A randomised prospective study of cadaver donor pretreatment in renal transplantation. *Transplantation*: 25:287-9.

In this relatively small RCT (52 recipients) of renal transplants; deceased donors were randomised to 5 g methylprednisolone + 7 g cyclophosphamide compared to usual treatment. After 12 months there was no significant difference in graft survival, graft function or acute rejection.

Chatterjee *et al.* (1977). Pretreatment of cadaver donors with methylprednisolone in human renal allografts. *Surg Gyn Obst*. 145:729-32.

In this RCT 50 donors were randomised to receive 5 g methylprednisolone or standard treatment. There was no significant difference in the number of transplants or graft survival at 1 and 3 months after transplant.

Appendix 8. The use of thyroid hormones in the management of deceased donors

Summary of findings

Although many retrospective studies, including large registry studies, demonstrate improved organ recovery rates from donors treated with thyroid hormones, this benefit is not confirmed in any of the randomised controlled trials (RCTs) identified. None of these randomised studies demonstrate differences in haemodynamic parameters or stability in donors, or in post-transplant organ outcomes. This may be due to incomplete correction for confounding variables in retrospective studies, or due to a lack of power in the small RCTs identified.

Clinical question

'Does the intravenous administration of thyroid hormones to potential deceased organ donors improve transplant rates and/or transplant outcomes?'

PICOS

Population: Adult patients (aged 18 or over) admitted to an ITU with the diagnosis of death by neurological criteria, being considered as a potential organ donor.
Intervention: Administration of intravenous thyroid hormones in the ICU. Hormones include a dose of tri-iodothyronine (T_3) or thyroxine (T_4). Hormones can be administered in isolation, or as part of a combination therapy regimen.
Comparator: No hormone, placebo or alternative therapy (including alternative thyroid hormones or treatment combinations).
Outcomes: Primary outcome was the number of organs transplanted by donor. Secondary outcomes include proportion of potential donors proceeding to donation, graft function and measures of donor stability (e.g. inotrope use, cardiovascular parameters).
Study design: Systematic reviews or randomised controlled trials.

Search strategy and results

The Transplant Library (TL) was searched from inception to 20 May 2020. The TL includes all randomised controlled trials and systematic reviews in the field of solid organ transplantation published as full text or in abstract form, sourced from MEDLINE, EMBASE and the Cochrane Library.

The search strategy used is as follows:

1. exp THYROID HORMONES/
2. exp THYROXINE/
3. (T_3 or T_4 or thyro$ or triiodothyronine).ti,ab.
4. or/1-3

Searches identified 70 potentially relevant references; 16 references met the inclusion criteria defined above. Of these, 3 were systematic reviews, and 13 reported outcomes from 6 randomised controlled trials; 2 additional randomised controlled trials were identified from the reference lists of previous reviews.

Systematic reviews

Turco *et al.* (2019). Hormone replacement therapy in brain-dead organ donors: a comprehensive review

with an emphasis on traumatic brain injury. *The Journal of Trauma and Acute Care Surgery* 86(4): 702-9.

This narrative review identified 15 cohort studies, focussing on donors with traumatic brain injury. Rather than concentrating solely on thyroid hormones, the authors included all hormone replacement therapy with varying combinations of thyroid hormone, insulin and corticosteroids. They found that 93 % of studies demonstrated an increased organ procurement rate with hormone replacement therapy, although the effects of thyroid hormones in isolation are difficult to extract. It should be noted that this review appears to miss a number of the RCTs identified below.

Rech *et al.* (2013). Management of the brain-dead organ donor: a systematic review and meta-analysis. *Transplantation* 95(7): 966-74.

This systematic review looks at various aspects of donor management, including the use of thyroid hormones. The authors identified 6 studies exploring the use of thyroid hormones in donors. They meta-analyse 4 of these with cardiac index as an outcome, finding no difference in cardiac index between donors given thyroid hormone *versus* not. No other outcomes are subjected to meta-analysis, and the authors do not explore the impact on donation rates.

Macdonald *et al.* (2012). A systematic review and meta-analysis of clinical trials of thyroid hormone administration to brain dead potential organ donors. *Critical Care Medicine* 40(5): 1635-44.

This comprehensive review looks specifically at studies of thyroid hormone administration to brain-dead donors. The authors identify 37 studies – 16 cohort studies and 7 RCTs. Whereas retrospective studies (including some large registry-based studies) all demonstrated a benefit to thyroid hormone administration, the RCTs all conclude a lack of any measurable clinical benefit. The authors suggest that this may be due to a lack of correction for confounders in the non-randomised studies; it may also be due to lack of power in individual RCTs. It is worth noting that most RCTs included recruited potential cardiothoracic organ donors, rather than abdominal-organ alone donors, and very few donors in these studies were unstable.

Randomised controlled trials

Dhar *et al.* (2020). A randomized trial of intravenous thyroxine for brain-dead organ donors with impaired cardiac function. *Progress in Transplantation* 30(1): 48-55.

Dhar *et al.* (2019). A randomized trial comparing triiodothyronine (T3) with thyroxine (T4) for hemodynamically unstable brain-dead organ donors. *Clinical Transplantation* 33(3): e13486.

This is the only recent RCT published since the comprehensive review from Macdonald *et al.* (above). This small study randomised potential cardiac donors with impaired ejection fraction to T4 or not. Outcomes did not improve with T4, and organ recovery did not show a significant difference (although there was a trend towards increased donation rates in this small cohort).

Sharpe *et al.* (2013). Oral and intravenous thyroxine (T4) achieve comparable serum levels for hormonal resuscitation protocol in organ donors: a randomized double-blinded study. *Canadian Journal of Anaesthesia* 60(10): 998-1002.

This small Canadian study compares the use of oral and intravenous T4 in 32 potential organ donors. Vasopressor use, T3 and T4 levels and rates of organ recovery did not differ between groups, leading the authors to conclude that orally administered T4 is suitable as an alternative to intravenous T4 in the management of donors.

Venkateswaran *et al.* (2009). The haemodynamic effects of adjunctive hormone therapy in potential heart donors: a prospective randomized double-blind factorially designed controlled trial. *European Heart Journal* 30(14): 1771-80.

Venkateswaran *et al.* (2009). The proinflammatory environment in potential heart and lung donors: prevalence and impact of donor management and hormonal therapy. *Transplantation* 88(4): 582-8.

Venkateswaran *et al.* (2008). Early donor management increases the retrieval rate of lungs for transplantation. *Annals of Thoracic Surgery* 85(1): 278-86.

Venkateswaran *et al.* (2010). Echocardiography in the potential heart donor. *Transplantation* 89(7): 894-901.

James *et al.* (2010). The effects of acute triiodothyronine therapy on myocardial gene expression in brain stem dead cardiac donors. *Journal of Clinical Endocrinology & Metabolism* 95(3): 1338-43.

This study in potential lung donors takes a factorial design, comparing combinations of methyl-

prednisolone, tri-iodothyronine, both or placebo. There was no effect of intervention on lung or heart recovery, cardiac index or pulmonary function. Use of hormone replacement had no effect on biomarkers of inflammation.

Perez-Blanco *et al.* (2005). Efficiency of triiodothyronine treatment on organ donor hemodynamic management and adenine nucleotide concentration. *Intensive Care Medicine* 31(7): 943-8.

This small study of 52 potential donors randomised donors to IV tri-iodothyronine *versus* placebo. The investigators assessed haemodynamics, inotrope use and adenine nucleotides on biopsy of the extracted organs. No benefit was seen in the administration of tri-iodothyronine.

Goarin *et al.* (1996). The effects of triiodothyronine on hemodynamic status and cardiac function in potential heart donors. *Anesthesia & Analgesia* 83(1): 41-7.

This study investigates the use of IV T3 *versus* placebo in 37 DBD donors. The authors found no differences in cardiac function or haemodynamic function in patients treated with T3.

Randell and Hockerstedt (1992). Triiodothyronine treatment in brain-dead multiorgan donors–a controlled study [see comment]. *Transplantation* 54(4): 736-8.

Randell and Hockerstedt (1993). Triiodothyronine treatment is not indicated in brain-dead multiorgan donors: a controlled study. *Transplantation Proceedings* 25(1 Pt 2): 1552-3.

This early, small RCT from Helsinki randomised 25 potential donors to tri-iodothyronine or control. The authors found no benefit to tri-iodothyronine in donor haemodynamics or the outcomes of transplanted livers.

Mariot *et al.* (1991). Evaluation of tri-iodothyronine and cortisol treatment in the brain-dead patient. [in French]. *Annales françaises d'anesthésie et de réanimation* 10(4): 321-8.

This double-blind study randomised 40 potential donors to receive either T3 and cortisone or placebo. The authors found no difference in haemodynamic stability, metabolic profile or suitability for transplantation between groups.

Jeevanandam (1997). Triiodothyronine: spectrum of use in heart transplantation. *Thyroid*. 7(1):139-45.

The second part of this 3-part study randomised 30 potential donors to T3 administration or placebo. No differences were seen in donor stability or post-transplant function in liver or kidney recipients.

García-Fages *et al.* (1991). Effects of substitutive triiodothyronine therapy on intracellular nucleotide levels in donor organs. *Transplant Proc*. 23(5):2495-6.

García-Fages *et al.* (1993). Hemodynamic and metabolic effects of substitutive triiodothyronine therapy in organ donors. *Transplant Proc*. 25(6):3038-9.

This study in 44 potential donors investigates the use of T3. The main outcome was adenine nucleotide levels in explanted organs – increases were seen in kidney and pancreas, but not other organs. No differences in haemodynamic parameters were found between groups.

Appendix 9. The use of therapeutic hypothermia in the management of deceased donors

Summary of findings

There is extremely limited clinical evidence for the use of therapeutic hypothermia for donors following brain death. There is one randomised controlled trial (RCT) in renal transplantation, which does show a significant reduction in DGF, and this was a good quality RCT. The same effect on reducing DGF is supported by one large cohort study. There is no evidence that organ donation/transplant rates are improved by therapeutic donor hypothermia. There is no comparative data to support therapeutic hypothermia for non-renal organs, but it does not seem to be harmful taking the results of the sole RCT. Cohort studies analysing the impact of spontaneous donor hypothermia describe poorer heart allograft survival associated with spontaneous hypothermia, reduced eligibility for organ donation and reduction in organs per donor. However, it is likely that there are multiple confounders that make spontaneous hypothermia a very unreliable predictor for the effect of therapeutic hypothermia. The paucity of clinical evidence makes the one RCT even more impressive. Good quality RCTs will be needed to investigate the impact of therapeutic hypothermia on non-renal organs.

Clinical question

'Does therapeutic hypothermia of potential deceased organ donors improve transplant rates and/or transplant outcomes?'

PICOS

Population: Adult patients over the age of 18 admitted to an ICU with the diagnosis of death by neurological criteria as a potential organ donor.
Intervention: Therapeutic hypothermia.
Comparator: Normothermia, standard of care, no therapy, and different therapy.
Outcomes: The primary outcome will be the number of organs transplanted, by donor. The secondary outcomes will be early organ function (heart, lung, liver and kidney).
Study designs: Human studies only. RCTs, cohort studies, case-control studies, case series of more than 1 donor.

Search strategy and results

The Transplant Library (TL) was searched from inception to 28 July 2020. EMBASE was searched from 1974, and MEDLINE from 1946, to 28 July 2020. The TL includes all randomised controlled trials and systematic reviews in the field of solid organ transplantation published as full text or in abstract form, sourced from MEDLINE, EMBASE and the Cochrane Library.

The search strategy used is as follows:

1. Exp Organ Transplantation/
2. Exp Transplantation/
3. Donor .ti.ab OR donation .ti.ab
4. Hypotherm$ .ti.ab
5. exp Hypothermia, Induced/ or exp Hypothermia/

6. 1 OR 2
7. 4 OR 5
8. 3 AND 6 AND 7
9. Humans .sh
10. 8 AND 9

Searches identified 386 potentially relevant references. Only 4 references met the inclusion criteria defined above. Of these, none were systematic reviews, and 2 reported outcomes from just 1 randomised controlled trial. Three additional references described the results from 2 large cohort studies analysing **spontaneous donor hypothermia**, rather than therapeutic hypothermia. These have been described for comparison.

Systematic reviews

No systematic reviews were identified that met the inclusion criteria.

Randomised controlled trials

Niemann *et al.* (2015). Therapeutic hypothermia in deceased organ donors and kidney-graft function. *N Engl J Med*. 373(5): 405-14.

Malinoski *et al.* (2019). Therapeutic hypothermia in organ donors: follow-up and safety analysis. *Transplantation*. 103(11): e365-8.

This is a good quality RCT with maintained allocation concealment and modified intention-to-treat analysis (transplanted organs only). Donors received minor cooling to 34-35 degrees centigrade, with non-invasive cooling techniques, or were maintained at 36.5-37.5 degrees centigrade. There was a significant reduction in DGF rate for kidneys transplanted from the hypothermia group (28 %) compared to the normothermia group (39 %). The trial was stopped early by the data and safety monitoring board on the basis that efficacy had been demonstrated before completion of recruitment (370 donors enrolled, of 500 targeted). The greatest potential benefit was seen in expanded criteria donors, where the rate of DGF was significantly reduced from 57 % to 31 %. DGF in this study was defined as the need for any dialysis in the first week after transplantation. The overall rate of organs transplanted from the two study arms was similar. During the study period the organ procurement teams did not use hypothermic machine perfusion.

Follow-up data of 565 kidney, 262 liver, 94 heart, 99 lung and 25 pancreas transplants from donors included in this trial were obtained from national registries. There were no statistically significant differences in the adjusted and unadjusted 1-year kidney graft survival rates. However, a subgroup analysis by donor type showed that donor hypothermia was associated with higher 1-year graft survival in the subgroup of standard criteria donors. There were no significant differences in graft survival of other organs, which may be confounded by small numbers.

Cohort studies

Wright *et al.* (2019). The impact of therapeutic hypothermia used to treat anoxic brain injury after cardiopulmonary resuscitation on organ donation outcomes. Organ Donation Research Consortium (ODRC) Anoxic Organ Donor Study Group. *Ther Hypothermia Temp Manag*. Dec;9(4):258-64.

This is a large cohort study of 1 098 organ donors with hypoxic brain injury following CPR, 46 % of whom had received therapeutic hypothermia as part of their management prior to death, and these were compared to donors who did not receive this therapy prior to death. There was no significant increase in the number of organs transplanted from donors who received therapeutic hypothermia, except for a greater proportion of intestinal transplantation (8 % versus 5 %); 1-year graft survival for heart, lung, kidney and liver transplants was similar between groups. There was significantly less DGF in renal transplants from donors receiving therapeutic hypothermia (24 % versus 30 %). Multivariate analysis was conducted to adjust for potential confounding factors, and this showed an independent association between therapeutic hypothermia and reduced risk of DGF (OR = 0.75). DGF in this study was defined as the need for any dialysis in the first week after transplantation. The administration of therapeutic hypothermia was conducted by each donor hospital to their protocols and therefore may vary in terms of mean temperature and duration of cooling.

Schnuelle *et al.* (2018). Impact of spontaneous donor hypothermia on graft outcomes after kidney transplantation. *Am J Transplant*. Mar;18(3):704-14.

Schnuelle *et al.* (2018). Impact of donor core body temperature on graft survival after heart transplantation. *Transplantation*. Nov;102(11):1891-1900.

Spontaneous donor hypothermia study

This cohort study of 487 renal transplants and 99 heart transplants was conducted using data col-

lected during the randomised dopamine trial by the same group. Cox regression analysis was used to account for multiple confounding factors, and no independent association was found between spontaneous donor hypothermia (core body temperature < 36 degrees centigrade) and 5-year kidney graft survival. However, there was a significant reduction in DGF associated with spontaneous donor hypothermia in both the unadjusted and adjusted analyses (OR = 0.56 and OR = 0.42). DGF in this study was defined as 2 or more dialysis sessions post-operatively. In contrast to the beneficial effects on kidneys, lower core body temperature was associated with significantly inferior heart allograft survival. It should be noted that the lowest core body temperature category was as low as 32 degrees centigrade. Also the core body temperature was the last measurement taken prior to procurement, 4-20 hours beforehand, which may not represent the donor condition over a period of time. The 5-year follow-up completion was excellent (over 99 % of transplants); despite this the study is underpowered to detect a clinically significant reduction in graft survival for kidneys.

Joseph *et al.* (2014). Hypothermia in organ donation: a friend or foe? *The Journal of Trauma and Acute Care Surgery*. 77(4):559-63.

Spontaneous donor hypothermia study

This is a large registry analysis of all trauma patients approached for organ donation during a 5-year period at one centre in the USA. Donors were stratified by spontaneous hypothermia rather than therapeutic hypothermia; 416 patients were included, and hypothermia was defined as core body temperature less than 36 degrees centigrade. The study found that patients who were hypothermic on admission were significantly less likely to be eligible for organ donation (45 % *versus* 97 %) and donated fewer organs per donor (2.4 *versus* 2.8).

Case series

Baumgartner (1989). Cardiopulmonary bypass with profound hypothermia. An optimal preservation method for multiorgan procurement. *Transplantation*. 47(1):123-7.

In this case series, 10 brain dead donors were cooled to 10-15 degrees centigrade prior to dissection and retrieval of organs. The average time of bypass was 46 minutes (range 22-80 minutes); 10 heart-lung grafts, 17 kidneys, 1 liver and 1 pancreas were retrieved for transplantation. The paper focuses on the feasibility of the technique. Early transplant outcomes are presented in the paper, but there are no comparative data and the numbers are small.

Appendix 10. *Rationale document* for Medical and Social History Questionnaire (United Kingdom)

This appendix shows the *Rationale document* for the Medical and Social History Questionnaire (Information document INF947/6.1), including the questionnaire itself, as used in the United Kingdom since July 2019. The *Rationale document* is adjusted to all formal and informal rules valid in the healthcare system of the United Kingdom. In the healthcare systems of other member states, different formal and informal rules exist, and questionnaires must be adjusted to the rules that apply in their jurisdiction (e.g. see Appendix 12).

Rationale document for medical and social history questionnaire

Introduction

- The purpose of donor characterisation is to determine whether a potential donor is suitable to donate any organ or tissue, and then to determine which organs and tissue can be donated. Whilst, following assessment of an individual's medical and social history, organ and tissue donation may be possible, it may be that not all organs or tissues are suitable due to specific organ/tissue requirements.
- This document aims to provide a rationale for specific information that is required to assess a potential donor's suitability for organ/tissue donation and should be used in conjunction with the NHS Blood and Transplant FRM4211 Medical and Social History Questionnaire (MaSH).
- The purpose of the MaSH questionnaire is to collate relevant information for donor characterisation; this can help determine risk factors for the transmission of disease from donor to recipient. It is the responsibility of the Specialist Nurse Organ Donation/Specialist Nurse Tissue Donation/Tissue Donor Co-ordinator to collect comprehensive information on medical, behavioural and travel history and relay all the information obtained to the organ recipient and tissue procurement centres. In addition, for organs it is the responsibility of the implanting surgeon to assess the risk–benefit of transplant for their individual patients. For tissue, the final decision on donor acceptance is often made after reviewing additional information available post-donation and it is the responsibility of the tissue establishment to make the final decision on donor suitability.
- All specialist nursing staff trained to use this document must recognise when to expand questions in order to obtain more details, what additional information might be required and when to seek advice. It is expected that the donors referred for tissue donation meet donor selection guidelines (see link below) or have had an individual risk assessment on donor suitability.
- The conditions which will cause the deferral of a potential donation vary significantly between organs and tissue, including ocular tissue. For many of the questions asked, the principle will be to gain as much relevant information as pos-

sible, clearly document the information and inform recipient centres. For tissue donation this is also relevant; however, suitability can also be confirmed by reference to the current version of the UK Blood Transfusion Services document Tissue Donor Selection Guidelines for Deceased Donors (TDSG-DD).

- This rationale is a guide and should not replace discussions with transplant centres, tissue establishments, microbiologists and other experts where necessary. The Advisory Committee for the Safety of Blood, Tissues and Organs (SaBTO) guidance on the microbiological safety of human organs, tissue and cells used in transplantation will also provide more information on many of the questions below.

Patient assessment section

Whilst the MaSH document does give 'unknown' as an option to minimise organ/tissue deferrals, it is preferred wherever possible this option is not used. As such when opening the conversation with the family we request they answer with 'yes' or 'no'. In terms of the country of residence question, you are classed as a resident if you have lived somewhere for 6 months and over.

Question	Reason for asking the question	Additional action to take re organ donation	Additional action to take re tissue donation
FOR PAEDIATRIC DONATION: has your child been breast-fed in the past 12 months?	There is a risk of vertical transmission of some blood-borne viral infections from the mother to her child via breast milk. Although testing of the milk donor would be desirable, it is acknowledged that this may not be possible and this should not be a contra-indication for donation; discuss accordingly. Transplant centres should be informed. Prior to donating breast milk, microbiological screening will have been carried out in the maternity unit.	The mother's medical, social and behavioural history should be assessed and both a maternal and infant blood sample must be taken for full microbiological screening.	As organ donation.
NOTE: for all patients under the age of 18 months and any child who has been breast-fed in the last 12 months, a blood sample for microbiological testing is required from the mother, as well as from the patient.	Some infections can be transmitted from the mother *in utero*, at birth, perinatally and through breast feeding. Examples of some of those blood-borne viruses, which are also transmissible by transplantation, are CMV, HIV, HBV, HTLV and HCV. Testing the mother identifies potential infectious risk for the baby and if positive, will inform need for further testing in the case of organ donation; for tissue donation, a positive maternal result is a contra-indication for infant donation. (See additional action on the right). Donor characterisation testing portfolio has expanded over time; to avoid difficulties in obtaining sufficient blood sample from small babies, there are instances when a maternal sample can be used as a surrogate.	In the case of deceased neonatal or infant tissue donors the following blood samples are required: • A maternal sample is required when an infant is less than 18 months of age or when an older child has been breast fed within the 12-month period prior to donation. • For still births and neonates less than 48 hours after birth, no sample is required. • For neonates between 48 hours and 28 days after birth, a sample is only required if there are identifiable risks of possible viral transmission, e.g. receiving blood components/products or undergoing a surgical procedure. • For infants more than 28 days after birth, a sample is always required.	As organ donation. Under EU Tissues and Cells Directive, *if the mother is infected with HIV/HBV/HCV/HTLV or is at risk of these infections*, an infant under the age of 18 months or who has been breastfed in the past 12 months *cannot be accepted as a tissue donor*, regardless of the results of the tests; maternal sample is required to establish mother's status and assess donor suitability.
For ALL female patients aged between 12 and 55 years of age Is there a possibility that your relative could be pregnant?	There is a requirement to establish pregnancy status in female organ donors; this is standard best practice for females of childbearing age undergoing surgery.	If pregnancy is confirmed or suspected, the donation process should be paused, and expert advice should be sought to enable individual case assessment.	No action required.
General health information			
Was/did your relative or you (if completing as mother of paediatric donor):			

Question	Reason for asking the question	Additional action to take re organ donation	Additional action to take re tissue donation
1. Did your relative visit a general practitioner in the last two years? 2. Was your relative currently seeing or waiting to see a general practitioner or any other healthcare professional?	These are broad questions to ascertain if there are any long-term/current health problems. If the answer to either is yes, it is important to obtain as much information as possible including symptoms, diagnosis, investigations and medications prescribed; include names of hospitals if relevant to allow further clarification as required. Note: It is important to obtain accurate information on past/current medical history. Therefore, it is a requirement that the GP is contacted to complete the NHSBT GP questionnaire (FRM1602).	Attempts should always be made to contact the GP prior to the retrieval of organs. If following these attempts, the GP cannot be contacted, the NHSBT GP assessment MUST be sent by the next working day. Any new relevant information must be shared appropriately. If the patient has no GP then ensure this information is documented for recipient centres to be aware.	As organ donation.
3. Did your relative ever take regular medication?	This is a broad question to ascertain if there are any long-term/current health problems. Include type of medication, length of therapy and reason for treatment. Rationale for acne, prostate and psoriasis medication: Finasteride (prostate), Dutasteride (Avodart) or one of the following acne treatments: roaccutane, etretinate, acitretin, isotretinoin, alitretinoin, tamoxifen and dutasteride – All these medications are teratogenic and are excreted from the body at different rates at different times and can therefore be transmitted through tissue.	Document information clearly to alert accepting surgeons.	Refer to TDSG-DD guidelines re deferral period required for each of the named drugs – if donation will take place beyond the deferral period, accept donation; if donation takes place within the deferral period for the medication, defer donor unless the tissue bank can perform individual risk assessment based on risk–benefit analysis.
4a. Did your relative have a history of allergies to medication, food or other substances?	Aiming to establish all substances that the donor was allergic to; if the donor does have a history of allergy it is important to get information as to the type of allergy i.e. mild rash or severe anaphylactic type reaction. There is the potential that the organ recipient would develop the same type of allergy as the donor.	Document information clearly to alert accepting surgeons.	No action required.
4b. Did your relative have any health problems due to exposure to toxic substances such as pesticides, lead, mercury, gold, asbestos, cyanide, agent orange etc?	Some toxic substances may linger in the body for several years and could potentially be transmitted through transplanted tissue/organs.	Document information clearly to alert accepting surgeons.	It is HTA requirement based on EU Commission Directive 2006/17/EC that tissue donation from donors with the history of "ingestion of or exposure to a substance (such as cyanide, mercury, lead, gold) that may be transmitted to recipients in a dose that could endanger their life" must be excluded. Expert advice must be sought for individual risk assessment.
5a. Was your relative a diabetic? If yes, were they on insulin? 5b. Is there a family history of diabetes? If yes, is it insulin-dependent diabetes?	Because diabetes can have an effect on a number of organs particularly development of diabetic nephropathy in the kidneys, this information helps inform transplant centres when considering organs for transplantation. Increased risk of kidney disease runs in families.	If yes, absolute contraindication for pancreas and islet donation. Refer to POL188 (Contraindications to Organ Donation).	If yes, absolute contraindication for pancreas and islet donation No action required for other tissues.
6. Did your relative suffer from any chronic or autoimmune illness or disease of unknown cause?	Some diseases of unknown aetiology, such as multiple sclerosis, inflammatory bowel and Crohn's disease, may have an as yet unrecognised infectious cause. More importantly, if there is a current condition that is suspected to be of infectious origin but a cause has not been identified, there is a risk of transmission. Some chronic neurological or cardiac conditions for instance, may have an infectious aetiology which is unsuspected at time of death such as Chagas disease, a condition that is not commonly considered in the UK as it is not endemic.	Clinical assessment as appropriate. In light of other relevant information, including epidemiology; e.g. family or own history of gastro intestinal dysmotility, cardiac arrhythmia and residency in Chagas endemic area.	If answer yes to this question refer to current TDSG-DD as tissue donation may be contraindicated.

Question	Reason for asking the question	Additional action to take re organ donation	Additional action to take re tissue donation
7. Did your relative ever suffer from any bone, joint, skin or heart disease?	Responses will inform transplant centres and tissue establishments when assessing the patient's suitability to donate.	Document information clearly to alert accepting surgeons.	If answer yes to this question refer to current TDSG-DD as tissue donation may be contraindicated.
8. Did your relative ever have hepatitis, jaundice or liver disease?	Jaundice can have infectious causes, such as viral hepatitis, and non-infectious causes, such as gallstones. Enquire regarding dates, causes, diagnosis, investigations.	Document information clearly to alert accepting surgeons.	If answer yes to this question refer to current TDSG-DD as tissue donation may be contraindicated.
9. Did your relative recently suffer from significant unplanned weight loss?	Recent unplanned weight loss may be an indication of illness, including malignancy. It is important therefore to obtain the reason for the weight loss, the estimated amount of weight loss, if it was investigated or accompanied by other problems.	Document weight loss information clearly to alert accepting surgeons.	As organ donation.
10. Did your relative ever undergo any investigations for cancer or were they ever diagnosed with cancer?	The presence, or previous history, of malignancy poses a risk of transmission of malignant cells to a recipient. If yes, obtain further information regarding dates, diagnosis and treatments. If investigations such as mammograms, smear tests, PSA testing for prostate cancer and so on have been completed, ensure it is clearly stated whether these were part of routine national screening or due to any concerns or symptoms to allow a risk–benefit assessment of the likely implications.	It is important to assess the type, grade and time scales of any malignancy, as certain types are contraindicated in organ donation. Refer to POL188 (Contraindications to Organ Donation).	If organ and tissue donation is contraindicated, corneal donation may be possible. Refer to current version of TDSG-DD.
11. Did your relative have a history of eye disease, receive any medications for eye problems (e.g. eye drops) or undergo eye surgery or laser treatment?	This question is specifically designed to assess the suitability of ocular tissue; note that glaucoma surgery might involve the use of allogeneic scleral tissue and it is therefore important to elicit whether a patient with glaucoma has undergone surgery and where, even if further surgical details are not known to the family at the time of the family interview	Not applicable to organ donation	If answer yes to this question refer to current TDSG-DD as donation may be contraindicated.
12. Did your relative ever have any operations?	If the answer is yes, it is important to obtain as much information as possible, such as reasons for surgery, as this may provide important past medical history. In particular. any operations for malignancy, neurosurgery or operations where organs/tissue were transplanted.	Document information clearly to alert accepting surgeons.	If answer yes to this question refer to current TDSG-DD as tissue donation may be contraindicated.
13. Did your relative ever have any surgery on the brain or spine?	Before 1993 *dura mater* from deceased donors, which has been documented to transmit CJD, may have been used in brain and spinal surgery. Therefore where this answer is yes, the patient is at increased risk of CJD. Clarity should be sought on type of procedure, dates and location/hospital where procedure occurred.	Document information clearly to alert accepting surgeons.	If answer yes to this question refer to current TDSG-DD as tissue donation may be contraindicated.
14. Did your relative ever have an organ or tissue transplant?	This will provide information regarding any previous requirement of immunosuppression or risk of CJD transmission if within specific time frames, and will inform decision making.	Document information clearly to alert accepting surgeons.	If answer yes to this question refer to current TDSG-DD as tissue donation may be contraindicated.
15. Was your relative ever told not to donate blood?	If answered yes, reason for this must be clarified. Some deferrals are due to reasons such as a patient's age or weight; however, there may be other reasons such as infection risk, including being at CJD risk for public health purposes.	Document information clearly to alert accepting surgeons.	If answer yes to this question refer to current TDSG-DD as tissue donation may be contraindicated.

Question	Reason for asking the question	Additional action to take re organ donation	Additional action to take re tissue donation
16. Did your relative receive a transfusion of blood or blood product(s) at any time?	This should include type of product, such as Fresh Frozen Plasma (FFP), Platelet, Cryoprecipitate or Immunoglobulin as these are human derived products. The reason for the transfusion should also be obtained as this may provide significant medical history. Establish in which country the transfusion occurred as donor screening policies vary by date and country and this information is helpful. Transfusions have been known to transmit bacterial, viral, protozoal and prion infections, such as variant CJD. Testing of blood donors for markers of infection varies by country and by date, so level of risk will also vary. Please document all transfusions given during this admission, as well as historical transfusions if known.	Any transfusions should be noted and the laboratory completing the microbiology testing should be informed if the potential donor received any transfusions within the last 3 months. Antibodies can be acquired passively through transfusions so a positive antibody test in a post-transfusion sample may need to be interpreted accordingly. The laboratory interpretation must take this into account and the information should be passed on to the transplant centres. Transfusion history should be explored as part of the review of medical records and importantly the prescription chart for the current admission (NB if a potential donor has had more than one admission within the 3 days prior to the current, then prescription charts for these admissions should also be reviewed). Documenting all transfusions (not just the ones relevant for haemodilution calculation) would give a full picture should there ever be the need to investigate a potential transfusion-transmitted infection.	As organ donation.
17. Did your relative suffer from any type of brain disease such as Parkinson's or Alzheimer's disease, or dementia?	Neurological disease may be of infectious or non-infectious origin or a neurodegenerative condition of unknown aetiology e.g. Parkinson's disease or Alzheimer's disease.	Not applicable to organ donation.	If answer yes to this question refer to current TDSG-DD as tissue donation may be contraindicated.
18. (A-D) Did your relative suffer from any one or more of the following problems: memory problems or confusion, change in personality or behaviour, or were they unsteady on their feet?	CNS conditions have a range of underlying pathologies, and for the purposes of organ and tissue donation it is important to identify and exclude those that might be of infectious origin or of unknown aetiology such as neurodegenerative conditions (e.g. Parkinson's disease or Alzheimer's disease). As relevant CNS conditions are not necessarily always fully diagnosed at time of death, it is important to identify potentially relevant clinical signs and symptoms as possible indicators of relevant disease processes. Slowly progressive neurological symptoms, including paraparesis, may have a yet undiagnosed viral aetiology (e.g. HTLV). New symptoms such as behavioural changes, confusion with or without fever and other symptoms, may be part of a yet undiagnosed infectious CNS process. It is important to establish time of onset, duration, severity and trend of neurological and psychiatric symptoms in order to assess their relevance. For example, patients with sporadic CJD would be expected to deteriorate noticeably from month to month. Being unable to live independently is a good indication of severity of any neurological condition, e.g. a patient with dementia is usually unable to live on their own. Clinical assessment will exclude other relevant underlying conditions that may also be present beside the primary cause of death (e.g. altered behaviour of new onset, which may be infectious in origin, followed by a fall or RTA). The cause of death may not be a deferral for donation; however, the underlying, as yet undiagnosed condition may have led to the incident leading to death.	Not applicable to organ donation.	If answer yes to this question refer to current TDSG-DD as tissue donation may be contraindicated.

Question	Reason for asking the question	Additional action to take re organ donation	Additional action to take re tissue donation
19. Did your relative have a family history of prion disease, such as CJD, or were they ever told that they were at risk of prion disease?	Individuals at familial risk of prion-associated disease are those who have two or more blood relatives with a prion-associated disease or where the family has been informed they are at risk following genetic testing and counselling. These patients are at increased risk of prion disease transmission.	Assessment must be made on a case-by-case basis and expert advice sought where necessary. 'At risk' and familial history are not an absolute contraindication to organ donation. Refer to POL188 (Contraindications to Organ Donation).	If answer yes, patient is contraindicated for tissue donation. If the donor has had genetic testing and been found not to be at risk for prion disease – accept.
20. Did your relative ever receive human pituitary extracts, e.g. growth hormones or fertility treatment or test injections for hormone imbalance?	Human pituitary extracts have been known to have been contaminated and have led to the transmission of CJD. They have not been used in the UK since 1985; however, it is uncertain when their use was stopped in other countries. Metrodin HP was an infertility treatment used up to 2003. However, patients treated after 2003 will not have been treated with this. Metrodin HP was manufactured from urine (sourced in Italy) and therefore was a risk of CJD. Donated eggs are classed as tissue donation due to the risk of CJD transmission.	Document information clearly to alert accepting surgeons.	If answer yes to this question refer to current TDSG-DD as tissue donation may be contraindicated.
21. Did your relative ever have any significant infection?	Significant infections can be regarded as any infection where an individual has required investigations, hospitalisation or a specialist referral. Infections identified in this section may be transmissible during transplantation depending on the detail. Therefore it is important to ascertain diagnosis, treatments and dates.	Refer to POL188 (Contraindications to Organ Donation). Initiate discussions at early stages, as appropriate.	If answer yes to this question refer to current TDSG-DD as tissue donation may be contraindicated.
22. Did your relative come into contact with an individual with an infectious disease within the last month?	Potential donors who have been in recent contact with an infectious disease may be in the asymptomatic stage of an infection at the time of donation. It is also helpful to know what type of contact the patient had.	Initiate discussions at early stages, as appropriate.	If answer yes to this question refer to current TDSG-DD as tissue donation may be contraindicated.
23. Did your relative have any signs of infection, e.g. colds, flu, fever, night sweats, swollen glands, diarrhoea, vomiting or skin rash within the last month?	Answers to this question will add to the clinical picture. It is important to enquire as to any treatment given, investigations, duration of illness. Further investigations may be required.	Initiate discussions at early stages, as appropriate.	Night sweats may be secondary to menopausal symptoms – having this information documented is important as this type of night sweats allows the tissue to be released.
24. Did your relative have any immunisations within the last 2 months?	Immunisations with live vaccine may cause severe illness in people who are immunosuppressed. By eight weeks any infection caused by the immunisation should have been controlled and so should not be passed on through donated organs or tissues. Very recent vaccination with HBV vaccine for instance (7 days) can give positive result for HBsAg during screening, which does not mean infection. (No other vaccines affect the result of routine donor characterisation tests.) Asking for type of flu vaccination (i.e. injection versus nasal spray) will help confirm whether the vaccination used was inactivated or a live vaccine. List of common live and inactivated vaccines should be checked at: https://www.transfusionguidelines.org/dsg/ctd/appendicies/appendix-4-table-of-immunizations.	Laboratory completing the donor microbiological screen must be informed if recent HBV vaccination.	As organ donation.

Question	Reason for asking the question	Additional action to take re organ donation	Additional action to take re tissue donation
25. Did your relative have tattooing, body piercing, botox injections, acupuncture, colonic irrigation, faecal transplantation or any other cosmetic treatments that involve piercing the skin in the last 3 months?	Any piercing of the skin for these reasons may carry a risk of viral disease transmission depending on the standards of practice. It is important to confirm when and where the treatment has been carried out, i.e. in the UK or not, and whether in licensed premises or not. If carried out in certain establishments, i.e. NHS or otherwise licensed establishments, tissue donation will be possible. During the 3-month period, if infection has occurred, it may not be detected by serological tests (window period). Colonic irrigation may be unregulated if not on NHS; as such there may be an increased risk of rectal mucosa damage and infection. Faecal microbiota – this is one of a number of treatments that can be done through the NHS or non-NHS – it is human derived and so has risk of blood-borne virus. Microblading and Microneedling – these procedures have become more popular in recent years and involve piercing of the skin. Unclear licensing requirements of people who carry out these procedures. Consideration must be given to all cosmetic procedures which may pierce the skin.	Document information clearly to alert accepting surgeons. Include relevant information in the virology request form to aid interpretation of results.	If answer yes to this question refer to current TDSG-DD as tissue donation may be contraindicated depending on where and when this happened. If faecal microbiota is carried out in the NHS or by a registered professional, so we know the donor is being screened and tested, then accept the donor; if done outside the NHS/not by a registered professional then defer if the treatment was in the last 3 months – if more than 3 months ago accept. If the donor or donor family state that tattoo/body piercing etc. was done in a high-street shop, we assume the shop is abiding by the law and is therefore licensed – there is no need to look for further evidence as to whether the shop was licensed or not.

Question	Reason for asking the question	Additional action to take re organ donation	Additional action to take re tissue donation
26. In the last 12 months has your relative been bitten or scratched by any animal (strays, pets, wild, farm or ticks) or been bitten by a human. Or, has your relative ever been bitten or in close contact with bats anywhere in the world or been bitten by a mammal outside the UK?	Exposure to animal secretions (e.g. bites or exposure to saliva through broken skin) may result in infections, for example rabies. In the UK the risk of rabies comes from contact with infected bats. Outside the UK, bites and scratches from infected mammals (most commonly dogs and cats but any mammal can get infected – see below) can be a source of rabies in endemic countries. A potential exposure to rabies is significant at any time so, if the patient's family mentions a significant exposure, obtain information regardless of time elapsed. Close contact with animals, including domestic family pets, may lead to zoonotic infections (infections transmitted between animals and humans), which may then be transmitted through transplantation. A significant number of families will have family pets. The main risk is if the donor has been bitten by an animal or there has been unusual contact between an animal (particularly if unwell) and the donor. Exposure to bats: In the UK, bat handlers are encouraged to receive rabies vaccination. Exposure is regarded as direct contact of bat saliva or neuronal tissue with broken skin or mucosa. If a bat is found in the room of a sleeping, previously sleeping or intoxicated person or child, this is classed as exposure as the person may not be aware they have been bitten and bites may not be visible. Otherwise, just being close to a bat does not constitute an exposure. Exposure to terrestrial (predominantly land living) mammals: Knowledge of any transdermal bite or scratch, lick to broken skin, contact of saliva with mucous membranes requires further discussion. Examples of animals known to have transmitted rabies: racoons, foxes, monkeys. Transmission of rabies through transplantation has been described when diagnosis of rabies in the donor had been missed despite presence of compatible signs and symptoms at the time of death. Tick bites can transfer infections, e.g. the agents that cause Lyme's disease, tick-borne encephalitis etc.	If the answer to this question is yes, as much information as possible must be ascertained. Important questions to ask include: Place of incident (country, region, area). Type of animal (raccoon, skunk, fox, etc). What was the injury (bite, scratch, lick to broken skin, mucosal exposure to saliva?) When did it happen? Was the animal vaccinated against rabies? Was the animal observed by anyone in the 14 days following the incident (animals with active rabies would die within 2 weeks)? Circumstances of incident - e.g. Was the bat dead or alive? Was the dog bite provoked or unprovoked? Was it directly on bare, broken or unbroken skin? Was any medical advice sought afterwards? Any treatment? (e.g. rabies hyperimmunoglobulin and rabies vaccine). Would anyone else have further information or have witnessed the incident?	Tissue donation is contraindicated if the patient has ever been bitten by a non-human primate, has any animal bite where the wound is infected or not healed, or if it is less than 12 months since being bitten anywhere in the world by any mammal outside the British Isles. Refer to current TDSG-DD.

Travel risk assessment

This group of questions is designed to establish the risks of a potential donor being/having been at risk of an infection which is not endemic within the UK. Due to the evolving patterns of infections worldwide, when a detailed travel history has been obtained it is necessary to consult both the TDSG-DD at www.transfusionguidelines.org/dsg/ctd and the Geographical Disease Risk Index (GDRI) at www.transfusionguidelines.org.uk/dsg/gdri for up-to-date information on the risk assessment criteria. It is the responsibility of the specialist nursing staff to gather appropriate information, including date, duration of travel, destination and purpose of trip; and whether the donor was well or unwell during their travel and on returning to the UK – the travel-associated risk may vary by region with some countries, e.g. malaria risk only in some parts of Türkiye or Zika risk in the USA. It is important to get as much information as possible, to document it and communicate it to transplant centres.

Question	Reason for asking the question	Additional action to take re organ donation	Additional action to take re tissue donation
27. Did your relative ever travel or live outside the UK (including business trips)?	Certain infections are distributed geographically and the risk of exposure will depend on the length of time and activities performed in the area. For some infections, risk is highest for residents of endemic areas (e.g. malaria and Chagas), regardless of how long ago they have left the area. Individuals who have lived in malaria-affected areas, particularly from early age, may develop a partial immunity to malaria through repeated exposure; they very often have no symptoms, despite infection being present. The malaria antibody screening test will identify that the donor had infection at some point; a NAT test will identify detectable parasite in the blood at the time of donation. In general terms, most risk of tropical acute infections such as Dengue, Chikungunya and Zika exists during the 4 weeks after return from endemic areas, hence dates of recent travel are an important part of the risk assessment.	Due to continually changing guidance in relation to this aspect refer to current GDRI. Document if any additional tests are being processed. Initiate discussions at early stages, as appropriate.	Due to continually changing guidance in relation to this aspect refer to current TDSG-DD and GDRI.
28. In the last 12 months, did your relative travel outside the UK (including business trips)?	Any travel within last 12 months may trigger further investigations for potential diseases such as malaria. Certain infections are distributed geographically and the risk of exposure will depend on the length of time and activities performed in the area. Full details are important, including area, dates, duration, nature of visit, type of activities.	Due to continually changing guidance in relation to travel refer to current GDRI. Document if any additional tests are being processed. Initiate discussions at early stages, as appropriate.	Due to continually changing guidance in relation to this aspect refer to current TDSG-DD and GDRI.
29. Did your relative ever have malaria or an unexplained fever which they could have picked up whilst abroad?	Malaria and other endemic infections such as West Nile Virus and *T. cruzi* can be transmitted by blood, organs, tissues and cells. Full details are required, including date and duration of visit, and any treatments or investigations undertaken.	Due to continually changing guidance in relation to this aspect refer to current GDRI. Document if any additional tests are being processed.	Due to continually changing guidance in relation to this aspect refer to current TDSG-DD and GDRI.
30. Was your relative unwell whilst abroad or in the first month on their return to the UK?	If patient was unwell while abroad or within 1 month of returning to the UK, the infection may have been contracted while abroad – depending on the country visited this may include infections that would require additional tests to be processed, or would contraindicate tissue donation, e.g. malaria, Zika, West Nile Virus etc. History of relevant epidemiology and symptoms are important and an individual risk assessment needs to be initiated as early as possible to enable appropriate discussions and any testing, if required.	Depending on country visited check GDRI to see what infection risk if any is linked with that country/region of country and decide whether additional tests are required e.g. malaria testing and discuss with transplant surgeons and document.	Due to continually changing guidance in relation to this aspect refer to current TDSG-DD and GDRI.
31. Did your relative ever live or travel outside the UK for a continuous period of 6 months or more?	Certain infections are distributed geographically and the risk of exposure will depend on the length of time and activities performed in the area. For some infections, risk is highest for residents of endemic areas, regardless of how long ago they have left the area. Individuals who have lived in a malaria-affected area, particularly from an early age, may develop a partial immunity to malaria through repeated exposure; they very often have no symptoms, despite infection being present.	Due to continually changing guidance in relation to this aspect refer to current GDRI. Document if any additional tests are being processed.	Due to continually changing guidance in relation to this aspect refer to current TDSG-DD and GDRI.

Question	Reason for asking the question	Additional action to take re organ donation	Additional action to take re tissue donation
32. Did your relative ever go to Central America, Mexico or South America for a continuous period of 1 month or more?	Individuals who have ever been in certain areas such as impoverished, rural communities (refer to SaBTO guidelines) of Central America, Mexico or South America for a period of 4 weeks or more may be at risk of *T. cruzi* infection. Full details are important including area, dates, duration, nature of visit, type of activities. For those who were born, or who have lived for a prolonged time or whose mothers were born in endemic areas for Chagas disease, family history or own history of cardiac (e.g. arrhythmia) or gastro-intestinal abnormalities are significant and should be noted.	Due to continually changing guidance in relation to this aspect refer to current GDRI. Document if any additional tests are being processed.	Due to continually changing guidance in relation to this aspect refer to current TDSG-DD and GDRI.
33. Was your relative's mother born in Central America, Mexico or South America?	*T. cruzi* infection can be passed vertically from mother to child so that a child born outside this area and who has never travelled to this area is still at risk of infection if their mother was born within the stated areas.	Document if any additional tests are being processed.	Due to continually changing guidance in relation to this aspect refer to current TDSG-DD and GDRI.
Behavioural risk assessment To the best of your knowledge did your relative:			
34a. Consume alcohol?	The effect of alcohol can impact on the quality of liver tissue. If yes, it is important to obtain as much information as possible. How much did the patient drink per day? What was it they drank (e.g. beer, spirits, wine etc)?	Document information clearly to alert accepting surgeons.	
34b. Smoke tobacco or any other substances?	Smoking in a donor is established to reduce both early and late survival after lung transplant. Current smoking is worse than past smoking. There is also a relation with extent of smoking history – i.e. pack-year totals, although this is less clearly defined. It is likely, by analogy to the decrease in cancer risk, that not smoking for more than 10 years largely equates to being a non-smoker, although there may already be structural damage to the lungs. If yes, it is important to obtain as much information as possible. How much did the patient smoke, what did they smoke and if they stopped smoking, when did they stop? Donor age, for lungs otherwise acceptable, does not appear to affect outcome until the donor is > 65, and even then the effect is small. The effect of advanced age is much less than the effect of smoking. As a result, it is now recognised that lifetime non-smokers, or those who have stopped for more than 10 years, are able to donate lungs up to the age of 75. Evidence suggests that E-cigarettes (such as vapers) are not harmful to lung tissue. Other substances – looking for evidence of precarious/risky behaviours if the patient is taking a substance that cannot be obtained legally.	Document information clearly to alert accepting surgeons.	
34c. Take any recreational drugs?	Looking for evidence of precarious/risky behaviours particularly if the patient is taking a substance that cannot be obtained legally.	Document information clearly to alert accepting surgeons.	Evidence of a potentially precarious/risky lifestyle – if only smoking cannabis, accept; if injected illegal drugs in the last 12 months, defer; if taking other oral recreational drugs would need a risk assessment.

Question	Reason for asking the question	Additional action to take re organ donation	Additional action to take re tissue donation
Based on information obtained from blood donors who tested positive and epidemiological data from larger populations, it is known that certain groups of people may be at increased risk of infection by HIV, HCV, HTLV and HBV. Unfortunately, it is not possible to exclude all cases of infection by relying on blood testing alone as infected donors may not be identified in the very early stages of infection, commonly referred to as the 'window period'. This refers to the period between being infected and the appropriate test being able to detect the infection. It takes several days/weeks for an infected individual to start forming antibodies, and a number of weeks before the antibody levels are high enough to be detected by using an antibody detection test; however, tests that are based on antigen detection will identify the infection earlier. During this window period the potential "negative" donor is infectious. The focus of this group of questions is to identify behavioural risks that can be associated with increased risk of infection. It is particularly important to note recent risks; whilst any established blood-borne infections will be detected through screening, very recent ones may not. Information must be passed on to the testing laboratory and transplant centres.			
35. Is it possible any of the following apply to your relative:			
35a. Was, or may have been, infected with HIV, hepatitis or HTLV?	These blood-borne viruses can all be transmitted via organ/tissue donation.	Refer to POL188 (Contraindications to organ donation).	If yes to this question tissue donation is contraindicated.
35b. Within the last 12 months have they injected or been injected with non-prescribed drugs, including performance-enhancing drugs or injectable tanning agents?	Individuals with a history of intravenous drug use remain the largest group diagnosed with HCV infection in the UK. They also have a higher rate of HIV and HBV infection. Ascertain if there was frequent exposure and dates of any exposure. Injectable tanning agents are illegal and their manufacture is not controlled.	Document information clearly to alert accepting surgeons.	Carry out risk assessment depending on the details provided.
35c. Been in prison or a juvenile detention centre for more than 3 consecutive days in the last 12 months? NB: This excludes those who have been in a police cell for < 96 hours.	Individuals in prison are at a higher risk of being exposed to transmissible viruses through sexual contact and intravenous drug abuse. Ascertain details of dates and duration.	Document information clearly to alert accepting surgeons.	If yes to this question tissue donation is contraindicated.
35d. Taken medication to prevent HIV infection, e.g. PrEP/pre-/post-exposure prophylaxis?	There is the potential for a significantly reduced antibody response to HIV in an HIV-infected individual taking PrEP – a low-titre infection (being treated) or a lower, blunted antibody response will mean that the HIV infection may be missed with current testing methods. This information must be passed to the testing laboratory and discussed at early stages as modification of the testing algorithm may be required.	This information must be passed to the testing laboratory and discussed at early stages as modification of the testing algorithm may be required.	As organ donation.
36. Has your relative ever had sex – consensual or otherwise?	This question needs to be asked of all donors irrespective of age. This includes the mother of neonates.	Document information clearly to alert accepting surgeons.	
If yes, is it possible that your relative:			
36a. Was given payment for sex with money or drugs in the last 3 months?	Individuals who receive payment for sex are at a higher risk of contracting HIV/HBV/HCV and other sexually transmitted diseases. The increased risk could be related to the high number of sexual partners, the potential promiscuity of these partners and possible drug-related habits.	Document information clearly to alert accepting surgeons.	If yes to this question tissue donation is contraindicated.
36b. Ever had a sexually transmitted infection?	If the answer is yes, ascertain type of infection, treatment and dates and where treated. Untreated STIs may eventually cause damage to many organs and tissues or could be transmitted to the recipient.	Document information clearly to alert accepting surgeons.	Acceptance criteria are specific for each condition; refer to current TDSG-DD.

Question	Reason for asking the question	Additional action to take re organ donation	Additional action to take re tissue donation
37. Did your relative have sex, consensual or otherwise in the last 3 months?		Document information clearly to alert accepting surgeons.	
If yes, is it possible that in the last 3 months your relative had sex with:			
37a. (For male patients only) another man?	Men who have sex with men have a much higher prevalence of HIV infection and other sexually transmitted diseases.	Document information clearly to alert accepting surgeons.	If yes to this question tissue donation is contraindicated.
37b. (For female patients only) a man who has ever had sex with another man?	The sexual partners of individuals who fall into the above category (37a) are at higher risk of HIV infection and other sexually transmitted diseases.	Document information clearly to alert accepting surgeons.	If yes to this question tissue donation is contraindicated.
37c. Anyone who is HIV- or HTLV-positive? 37d. Anyone who has hepatitis? 37e. Anyone who had a sexually transmitted disease? 37f. Anyone who has ever been given payment for sex with money or drugs? 37g. Anyone who in the last 12 months has injected, or been injected, with non-prescription drugs, including performance-enhancing drugs, injectable tanning agents?	Transmission of blood-borne sexually transmitted diseases is higher in individuals who fall into these categories.	Document information clearly to alert accepting surgeons.	Other than Q37i (see below) – If yes to any of these questions tissue donation is contraindicated.
37h. Anyone who may ever have had sex in a part of the world where AIDS/HIV is very common (this includes most countries in Africa)?	There is a higher risk of contracting some sexually transmitted infections in some parts of the world where they are more common.		
37i. Anyone who has developed an illness related to travel such as Zika?			If the donor has had sexual contact with anyone with a diagnosed infection in the previous 6 months, e.g. Zika, then there needs to be a risk assessment – when was the infection/ sexual contact, can we test, do we need to defer or can we accept based on the type of tissue
38. Having answered all the previous questions, is there anyone else who you think may provide more information?	The highest ranking/nearest relative may not be the person with the most relevant and current information to answer questions of a sensitive nature about the donor. If the answer is "yes" to this question, every effort should be made to identify and contact that individual to get the relevant information from that person as well.		

Medical and Social History Questionnaire in its original (2014) form

NHS
Blood and Transplant

Tissue Donor Number | | | | | | | | | | ODT Donor Number | | | | | | |

Medical and Social History Questionnaire

Directions for completion

1 This form must be completed in **black or dark blue ink** by the Specialist Nurse – Organ Donation (SNOD)/Specialist Nurse – Tissue Donation (SNTD)/Tissue Donor Co-ordinator (TDC) and signed where required.

2 The original copy should be retained by the **SNOD/SNTD/TDC** for the donor file.

3 A copy should be made for the patient's medical records.

4 In the event of organ and tissue donation, a legible copy should be sent to the relevant **Tissue Establishment**, where required.

NOTE: The term patient is used throughout the form to refer to the potential donor.

The term relative is used throughout the form to refer to the relationship between the patient and the interviewee.

In order to ensure the safety of organs and tissue for transplant I will need to ask you some questions about *(name of patient)* medical and lifestyle history. Some of the questions are of a sensitive and personal nature. They are similar questions to those asked when someone donates blood. I will read and discuss each question with you and ask that you answer to the best of your knowledge with either a "Yes" or "No."

PATIENT INFORMATION

Patient's Forename(s) Please print

Patient's Surname Please print

Donating Hospital

NHS/CHI Number

Cause of Death

Hospital Number

Date of Birth (dd/mm/yyyy)

Occupation

Country of Birth

Country of Residency

INTERVIEWEE INFORMATION

Information discussed with

Name Please print

Relationship Please print

For patients under the age of 18 months, or those who have been breast-fed or fed breast milk by a donor in the last 12 months, the mother is required to answer these questions with regard to her own and her child's health.

For children: has your child been breast-fed in the past 12 months? Yes ☐ No ☐ Unknown ☐

NOTE: for all patients under the age of 18 months and any child who has been breast-fed in the last 12 months, a blood sample for microbiological testing is required from the mother, as well as from the patient.

For ALL female patients between 13 and 53 years of age: Is there a possibility that your relative could be pregnant? Yes ☐ No ☐ Unknown ☐

GENERAL HEALTH INFORMATION

1. Did your relative visit a general practitioner in the last two years? Yes ☐ No ☐ Unknown ☐

If YES, give details

2. Was your relative currently seeing or waiting to see a general practitioner or any other healthcare professional? Yes ☐ No ☐ Unknown ☐

If YES, give details

3. Did your relative ever take regular medication? Yes ☐ No ☐ Unknown ☐

If YES, give details of any current or previous medication including any medication for acne, prostate or psoriasis

4a. Did your relative have a history of allergies to medication, food or other substances? Yes ☐ No ☐ Unknown ☐

If YES, please provide details of the substance they were allergic to and describe the reaction

4b. Did your relative have any health problems due to exposure to toxic substances such as pesticides, lead, mercury, gold, asbestos, agent orange etc? Yes ☐ No ☐ Unknown ☐

If YES, please provide details of the toxic substance and treatment

5a) Was your relative a diabetic? Yes ☐ No ☐ Unknown ☐

If YES, were they on insulin? Yes ☐ No ☐ Unknown ☐ N/A ☐

5b) Is there a family history of diabetes? Yes ☐ No ☐ Unknown ☐

If YES, is it insulin-dependent diabetes? Yes ☐ No ☐ Unknown ☐ N/A ☐

6. Did your relative suffer from any chronic or long term illness or disease? Yes ☐ No ☐ Unknown ☐

If YES, give details including hospital name and dates of treatment if possible

7. Did your relative ever suffer from any bone, joint, skin or heart disease? Yes ☐ No ☐ Unknown ☐

If YES, specify which and give details

8. Did your relative ever have hepatitis, jaundice or liver disease? Yes ☐ No ☐ Unknown ☐

If YES, give dates, diagnosis, treatment and hospital /clinic name if known

GENERAL HEALTH INFORMATION

9. Did your relative recently suffer from significant unplanned weight loss? Yes ☐ No ☐ Unknown ☐

If YES, give details

10. Did your relative ever undergo any investigations for cancer or were they ever diagnosed with cancer? Yes ☐ No ☐ Unknown ☐

If YES, give details including hospital name and dates of treatment, if possible

11. Did your relative have a history of eye disease, receive any medications for eye problems (e.g. eye drops), or undergo eye surgery or laser treatment? Yes ☐ No ☐ Unknown ☐

If YES, give details including hospital name and dates of treatment, if possible

12. Did your relative ever have any operations? ***If NO go to question 15*** Yes ☐ No ☐ Unknown ☐

If YES, give details including hospital name and dates of treatment, if possible

13. Did your relative ever have any surgery on the brain or spine? Yes ☐ No ☐ Unknown ☐ N/A ☐

If YES, give details including hospital name and dates of treatment if possible. **Surgery before 1993** is particularly significant

14. Did your relative ever have an organ or tissue transplant? Yes ☐ No ☐ Unknown ☐ N/A ☐

If YES, give details including hospital name and dates of treatment if known

15. Was your relative ever told not to donate blood? Yes ☐ No ☐ Unknown ☐

If YES, give details of where, when and the reason

16. Did your relative receive a transfusion of blood or blood product(s) at any time? Yes ☐ No ☐ Unknown ☐

If YES, give details including country, hospital name, dates and reason for transfusion

GENERAL HEALTH INFORMATION

17. Did your relative suffer from any type of brain disease such as Parkinson or Alzheimer disease or dementia? Yes ☐ No ☐ Unknown ☐

If YES, give details including hospital name and dates of treatment if possible

18. Did your relative suffer from any one or more of the following problems: memory problems or confusion, change in personality or behaviour, or were they unsteady on their feet? If **NO** go to Question 19, If **YES** Yes ☐ No ☐ Unknown ☐

18a. Were you aware of a condition causing these symptoms? Yes ☐ No ☐ Unknown ☐ N/A ☐

If YES, please specify condition

18b. When did these symptoms start?

Please give details

18c. Did they worsen noticeably over time?

Please give details

18d. Was your relative able to live independently?

Please give details

19. Did your relative have a family history of prion disease, such as CJD, or were they ever told that they were at risk of prion disease? Yes ☐ No ☐ Unknown ☐

If YES, please give details

20. Did your relative ever receive human pituitary extracts, e.g. growth hormones or for fertility treatment or test injections for hormone imbalance? Yes ☐ No ☐ Unknown ☐

If YES, give details including dates and hospital/clinic name if known

21. Did your relative ever have any significant infection? Yes ☐ No ☐ Unknown ☐

If YES, give details, and any treatment received and hospital/clinic name if known

RECENT HISTORY

22. Did your relative come into contact with an individual with an infectious disease within the last month? Yes ☐ No ☐ Unknown ☐

If YES, please specify details, dates, symptoms, diagnosis, and treatment

23. Did your relative have any signs of infection, e.g. colds, flu, fever, night sweats, swollen glands, diarrhoea, vomiting or skin rash within the last month? Yes ☐ No ☐ Unknown ☐

If YES, please specify dates, symptoms, diagnosis, and treatment

24. Did your relative have any immunisations within the last 2 months? Yes ☐ No ☐ Unknown ☐

If YES, give details including travel vaccinations and flu vaccination or flu nasal spray

25. Did your relative have tattooing, body piercing, botox injections, acupuncture colonic irrigation, faecal transplantation, or any other cosmetic treatments that involve piercing the skin in the last 3 months? Yes ☐ No ☐ Unknown ☐

If YES, give details including where and when including unlicensed clinics in UK or abroad

26. Has your relative ever been bitten or scratched by any animal including strays, pets, wild or farm. Or have they ever been bitten or in close contact with ticks or bats? Yes ☐ No ☐ Unknown ☐

If YES, give details of incident, circumstances, animal, place, dates, and treatment

TRAVEL HISTORY

27. Did your relative ever travel or live outside the UK (including business trips)? Yes ☐ No ☐ Unknown ☐
If NO go to question 33

28. In the last 12 months did your relative go outside the UK (including business trips)? Yes ☐ No ☐ Unknown ☐ N/A ☐

Give details of dates and destinations visited

29. Did your relative ever have malaria or an unexplained fever which they could have picked up whilst abroad? Yes ☐ No ☐ Unknown ☐ N/A ☐

If YES, give date of fever/illness, places visited, duration and dates

30. Was your relative ever unwell whilst abroad or in the first month of their return to the UK? Yes ☐ No ☐ Unknown ☐ N/A ☐

If YES, give details

31. Did your relative ever live or travel outside the UK for a continuous period of 6 months or more? Yes ☐ No ☐ Unknown ☐ N/A ☐

If YES, give details of dates and destinations

32. Did your relative ever go to Central America, Mexico or South America for a continuous period of 1 month or more? Yes ☐ No ☐ Unknown ☐ N/A ☐

If YES, give details of dates, places (remote/rural/urban areas), nature of visit

33. Was your relative's mother born in Central America, Mexico or South America? Yes ☐ No ☐ Unknown ☐ N/A ☐

If YES, give details

BEHAVIOURAL RISK ASSESSMENT

34. Did your relative
(a) Consume alcohol? Yes ☐ No ☐ Unknown ☐

If YES, give details

(b) Smoke tobacco or any other substance? Yes ☐ No ☐ Unknown ☐

If YES, give details of substance, frequency, history of smoking time and time elapsed since giving up.

(c) Take any recreational drugs? Yes ☐ No ☐ Unknown ☐

If YES, give details of route of administration and dates

35. Is it possible that any of the following apply to your relative?

(a) Was, or may have been infected with HIV, hepatitis or HTLV? Yes ☐ No ☐ Unknown ☐

(b) Within the last 12 months have they injected, or been injected, with non-prescription drugs, including performance enhancing drugs or injectable tanning agents? Yes ☐ No ☐ Unknown ☐

(c) Been in prison or a juvenile detention centre for more than 3 consecutive days? Yes ☐ No ☐ Unknown ☐

(d) Taken medication to prevent HIV infection e.g. (PrEP/ Post exposure prophylaxis)? Yes ☐ No ☐ Unknown ☐

If YES to any of the above questions a-d, give details, including dates for question c

36. Has your relative **ever** had sex – consensual or otherwise?
If no, go to question 38. If yes, is it possible that your relative: Yes ☐ No ☐ Unknown ☐

If **YES**, is it possible that your relative:

(a) Was given payment for sex with money or drugs in the last 3 months? Yes ☐ No ☐ Unknown ☐ N/A ☐

(b) Ever had a sexually transmitted disease? Yes ☐ No ☐ Unknown ☐ N/A ☐

If YES, give details, including hospital/clinics, dates, treatments.

37. Did your relative have sex, consensual or otherwise in the last 3 months?	Yes ☐	No ☐	Unknown ☐	N/A ☐
If no, go to question 38. If yes, is it possible that in the last 3 months your relative had sex with:				
(a) *(for male patients only)* another man?	Yes ☐	No ☐	Unknown ☐	N/A ☐
(b) *(for female patients only)* a man who has had sex with another man?	Yes ☐	No ☐	Unknown ☐	N/A ☐
(c) Anyone who is HIV or HTLV positive?	Yes ☐	No ☐	Unknown ☐	N/A ☐
(d) Anyone who has hepatitis?	Yes ☐	No ☐	Unknown ☐	N/A ☐
(e) Anyone who had a sexually transmitted disease?	Yes ☐	No ☐	Unknown ☐	N/A ☐
(f) Anyone who has ever been given payment for sex with money or drugs?	Yes ☐	No ☐	Unknown ☐	N/A ☐
(g) Anyone who in the last 12 months has injected or been injected with non-prescription drugs including performance enhancing drugs or injectable tanning agents?	Yes ☐	No ☐	Unknown ☐	N/A ☐
(h) Anyone who could have had sex, in any part of the world, where AIDS/HIV is very common (this includes most countries in Africa)?	Yes ☐	No ☐	Unknown ☐	N/A ☐
(i) Anyone who has developed an illness related to travel such as Zika?	Yes ☐	No ☐	Unknown ☐	N/A ☐
38. Having answered all the previous questions, is there anyone else who you think may provide more information?	Yes ☐	No ☐		

If YES, please specify

Question number	Relevant additional information. If any questions have been answered as unknown, give an explanation

Signature of healthcare professional obtaining information

Please print name

Designation of healthcare professional obtaining information

Date of interview

2 0

Time of interview

Appendix 11. **Donor patient history questionnaire (Germany, English-language version)**

	Patient's history questionnaire		
	identification		
	date and time		
	interviewer	☐ attending physician ☐ co-ordinator	
	kind of interview	☐ personal ☐ telephone	
	resources used	☐ hospital physician ☐ general practitioner ☐ donor relative ☐ other	
	any obstacles during interview		

1.	**Medical treatment (during past 12 months)**	☐ yes ☐ no ☐ unknown
	outpatient treatment	☐ yes ☐ no ☐ unknown
	contact data to outpatient treatment	
	reason for outpatient treatment	
	inpatient treatment	☐ yes ☐ no ☐ unknown
	contact data to inpatient treatment	
	reason for inpatient treatment	
	any transfusions during outpatient or inpatient treatment?	☐ yes ☐ no ☐ unknown
	if yes, where and indication	

2.	**Pre-existing illness/disease or past medical illness/previous surgery**	☐ **yes**	☐ **no**	☐ **unknown**
	diabetes*	☐ yes	☐ no	☐ unknown
	arterial hypertension*	☐ yes	☐ no	☐ unknown
	coronary artery disease*	☐ yes	☐ no	☐ unknown
	hepatitis/jaundice*	☐ yes	☐ no	☐ unknown
	tuberculosis*	☐ yes	☐ no	☐ unknown
	venereal disease or sexually transmitted disease*	☐ yes	☐ no	☐ unknown
	other infections (e.g. malaria)*	☐ yes	☐ no	☐ unknown
	breast tumour/malignancy*	☐ yes	☐ no	☐ unknown
	melanoma or skin tumour/malignancy*	☐ yes	☐ no	☐ unknown
	intestinal/colon tumour/malignancy*	☐ yes	☐ no	☐ unknown
	prostatic tumour/malignancy *	☐ yes	☐ no	☐ unknown
	gynaecological or obstetric tumour/malignancy*	☐ yes	☐ no	☐ unknown
	other tumour/malignancy*	☐ yes	☐ no	☐ unknown
	disease of central nervous system/neurological or psychiatric illness*	☐ yes	☐ no	☐ unknown
	autoimmune diseases*	☐ yes	☐ no	☐ unknown
	haematologic diseases/coagulation disorders	☐ yes	☐ no	☐ unknown
	if yes: received coagulation products of human origin*	☐ yes	☐ no	☐ unknown
	any other pre-illness*	☐ yes	☐ no	☐ unknown
	previous surgery*	☐ yes	☐ no	☐ unknown
	* if yes, specify details			

3.	**Medications/substance abuse/drugs/injections, etc.**			
	regular medications*	☐ yes	☐ no	☐ unknown
	if yes: specify *medication*			
	regular use of pain medications/analgesics	☐ yes	☐ no	☐ unknown
	smoking*	☐ yes	☐ no	☐ unknown
	if yes: *duration, amount (pack-years)*			
	alcohol abuse*	☐ yes	☐ no	☐ unknown
	if yes: *duration, amount*			
	injections without medical indication (iv, im, sc) during past 12 months*	☐ yes	☐ no	☐ unknown
	evidence for drugs consumed (e.g. stimulants, amphetamine, LSD, marijuana, cocaine)*	☐ yes	☐ no	☐ unknown
	drugs consumed iv/nasal*	☐ yes	☐ no	☐ unknown
	tattoos, piercings, acupuncture (during past 12 months)*	☐ yes	☐ no	☐ unknown
	* if yes, specify details			

4.	**Abnormality during past 12 months (B-Symptoms)**	☐ yes	☐ no	☐ unknown
	fever/unexplained fever attacks or elevation of body temperature	☐ yes	☐ no	☐ unknown
	night sweats	☐ yes	☐ no	☐ unknown
	headache	☐ yes	☐ no	☐ unknown
	loss of weight	☐ yes	☐ no	☐ unknown
	diarrhoea	☐ yes	☐ no	☐ unknown
	swelling of lymph nodes	☐ yes	☐ no	☐ unknown
	dysmenorrhoea/haemorrhage	☐ yes	☐ no	☐ unknown

5.	**Affiliation to at-risk group for recent HIV HBV HCV infection***			
	appropriate information not available*	☐		
	prostitution (during past 12 months)*	☐ yes	☐ no	☐ unknown
	frequently changing sexual partner (during past 12 months)*	☐ yes	☐ no	☐ unknown
	sexual partner with HIV, HBV or HCV infection or at-risk group (during past 12 months)*	☐ yes	☐ no	☐ unknown
	imprisonment (during past 12 months)*	☐ yes	☐ no	☐ unknown
	men who have sex with men (MSM) (during past 12 months)*	☐ yes	☐ no	☐ unknown
	children of mothers HIV-infected or at-risk group for HIV infection (especially < 18 months or breastfed during past 12 months)*	☐ yes	☐ no	☐ unknown
	long-term stay in area with high prevalence for HIV, HBV or HCV*	☐ yes	☐ no	☐ unknown
	other evidence for increased risk (e.g. contact to open wound/blood/mucosa of persons at risk for HIV, HCV, or HBV infection, *Treponema pallidum* antibody reactive or other window-period-infection)*	☐ yes	☐ no	☐ unknown
	* if yes, specify details			

6.	**Exclusion from blood donation***	☐ yes	☐ no	☐ unknown
	* if yes, specify (reason, bloodbank)			

7.	**Stay (during past 3 months) or immigration from outside northern or central Europe***	☐ yes	☐ no	☐ unknown
	* if yes, specify where, duration of stay			

8.	**Vaccinations (within the past 4 weeks)***	☐ yes	☐ no	☐ unknown
	if yes, please mark			
	☐ influenza (if inhaled)	☐ varicella	☐ tick-borne encephalitis	☐ rotavirus
	☐ polio (if oral)	☐ measles	☐ mumps	☐ rubella
	☐ cholera (if oral)	☐ yellow fever		
	☐ BCG	☐ smallpox	☐ *Salmonella typhi* (if oral)	☐ other

9.	**Multidrug resistant organisms**	☐ yes	☐ no	☐ unknown
	if yes, specify (what kind)			

10.	**Animal bite/injury by animal**	☐ yes	☐ no	☐ unknown
	if yes, specify which animal			

11.	**Exist signs of pregnancy**	☐ yes	☐ no	☐ unknown
	if yes, specify			

12.	Additional remarks	☐ yes ☐ no

Date and name of physician/signature _____

Date and name of donor co-ordinator/signature _____

This questionnaire aims to ensure that disease transmission risks are not missed although limitations may exist. If in any section a 'yes' is marked, the donor co-ordinator should initiate appropriate investigations in order to clarify whether risk factors for transmissible diseases exist or not in a particular donor.

Appendix 12. **Physical examination of an organ or tissue donor (Dutch Transplant Foundation)**

The rationale for this form is to standardise the physical examination for potential organ and tissue donors. This form is equivalent to the one shown in the EDQM *Guide to the quality and safety of tissues and cells for human application*, 4th edition, Appendi x 15. Table A12.1 (below) provides a rationale document for physical examination. [1, 2]

Table A12.1. **Rationale document for physical examination questionnaire**

Question/investigation	Reason for doing this	Additional action to take re donation
Weight/height/general condition/dietary condition	1. Exact measurements of body height and body weight (often possible) 2. Cachexia may be caused by malnutrition or other disease (e.g. cancer) 3. Overweight etc. may link to unknown metabolic disorders (e.g. diabetes, metabolic syndrome)	1. help to avoid size mismatch during allocation for recipients. 2. identify cause of cachexia or reason for compromised general condition 3. check for such diseases and secondary end organ damage
Abnormal ocular finding (e.g. leukoma, conjunctivitis)	Other diseases unidentified (e.g. cataract surgery, emerging viral infections, trachoma)	Identify reason (e.g. previous surgery, metabolic disease, cancer, infection)
White spots or other lesions in the mouth	E.g. unexplained infection such as candidiasis (examine in ventilated donor also if possible)	Identify reason
Jaundice or icterus (eye)	Impaired liver function or acute liver disease	Identify reason (e.g. acute hepatitis)
Scar at any place in the body	Surgical scars hint at previous surgery, which may have been previous oncologic surgery for treatment of cancer.	Identify reason; consider CT-scan pre-procurement, assess situs at procurement carefully with histopathological examination of any suspicious mass
Non-medical injection	Intravenous drug abuse or other non-sterile medical procedure	Consider non-standard risk for e.g. HIV, HBV or HCV, or other infection
Tattoo/piercing	Was this done within less than 6 months and if so under unsterile conditions?	Consider non-standard risk for e.g. HIV, HBV or HCV infection if twice yes
Rash/scab/skin lesion (non-anal) anywhere on body	Skin lesions are an indicator for multiple diseases (e.g. infection, skin cancer, melanoma)	Identify cause of skin lesion
Blue/purple (grey/black) spot/ lesion on skin anywhere on body	Orientating examination for skin cancer (e.g. melanoma) is better than doing nothing	In doubt apply ABCDE scheme (see Table B), initiate excision with histopathological examination or dermatologic examination
Haematoma, contusions, abrasion injury, fractures, etc.	1. Helps to explain trauma mechanism 2. E.g., haematoma may link to coagulation disorders	1. Check for damage to other organs 2. Check for further details

Question/investigation	Reason for doing this	Additional action to take re donation
Enlarged lymph nodes (e.g. palpation cervical, axilla, groin)	Undetected infection or cancer	Identify cause of lymph node enlargement
Enlarged liver, other space occupying lesion (SOL) in abdomen, thorax or mamma	Liver disease (e.g., acute hepatitis, but note: cirrhotic liver may not be enlarged). Other SOL suspicious for cancer etc.	Identify cause of liver disease and/or SOL (continue as suggested for scars).
Genital lesion (e.g. insertion trauma/peri-anal lesion/other lesions)	1. May be related to undisclosed lifestyle or sexual activity or e.g. abuse in children 2. undetected cancer	1. Consider non-standard risk for e.g. HIV, HBV, HCV infection transmitted sexually 1+2. requires further investigations

Donor identification:

Donor number:

Date of birth: Gender: M ☐ F ☐

Date recovery:

Identification verification: No ☐ Yes ☐

Consent: No ☐ Yes ☐

Recovery team members:

Start time recovery:

Eye tissue | Skin

Heart valves | MS tissue

Thoracic aorta | Femoral arteries

Complications during procedure: No ☐ Yes ☐

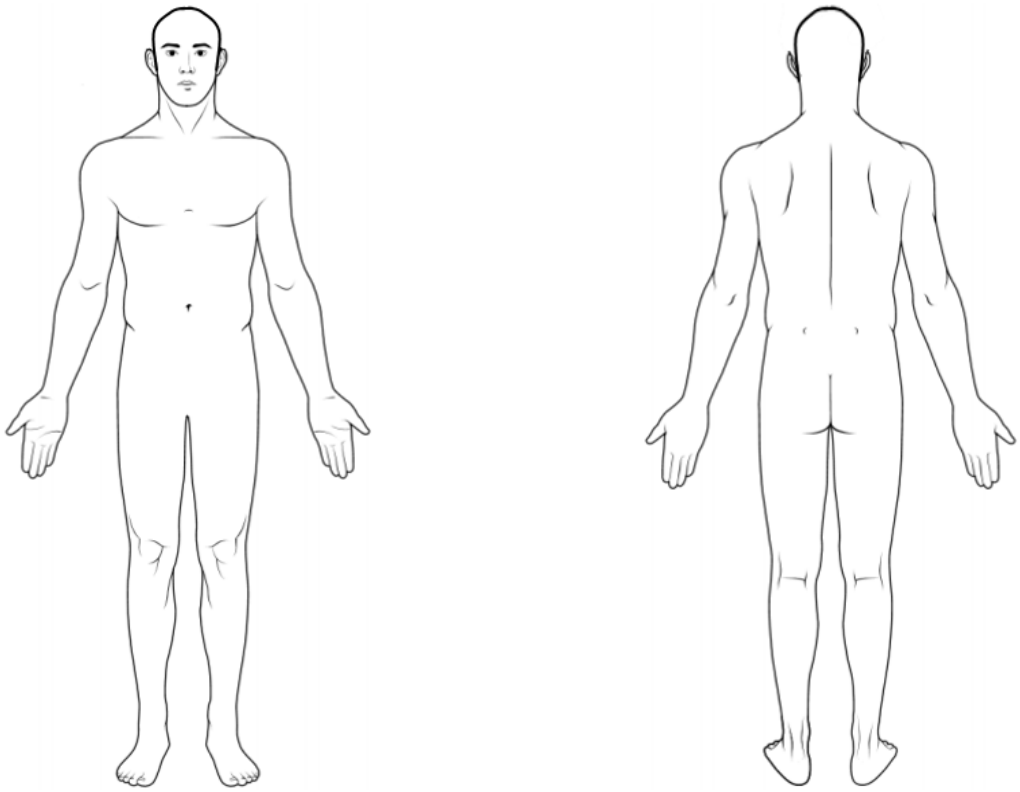
General appearance: Good ☐ Moderate ☐ Poor ☐

Height: cm Weight: kg

(O)	Ocular abnormalities	No ☐	Yes ☐	Unable to visualise ☐	
(WS)	White spots in the mouth	No ☐	Yes ☐	Unable to visualise ☐	
(J)	Jaundice	No ☐	Yes ☐		
(LN)	Abnormal lymph node(s)	No ☐	Yes ☐	Location? Size? Consistency?	
(L)	Enlarged liver	No ☐	Yes ☐		
(H)	Haematoma/bruises	No ☐	Yes ☐		
(GL/PL)	Genital and/or perianal lesions	No ☐	Yes ☐		
(NMI)	Non-medical injection sites	No ☐	Yes ☐		
(SL)	Skin lesions	No ☐	Yes ☐	Requires description	
(S)	Scars	No ☐	Yes ☐	Old ☐ Recent ☐	
(Ta/Pi)	Tattoos/piercings	No ☐	Yes ☐	Old ☐ Recent ☐	

(IV)	IV/Arterial line	(P)	Pacemaker/ICD	(BN)	Bone needle
(MP)	Needle entry site (medical procedures)	(D)	Drainage	(St)	Stoma

(BC)	Needle site blood collection	(C)	Cast	(Ca)	Catheter
(B)	Bandage	(I)	Autopsy/organ recovery incision	(De)	Decubitus



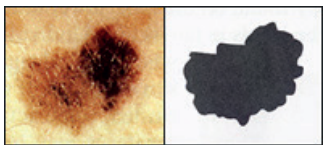
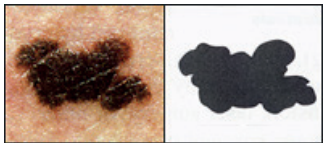
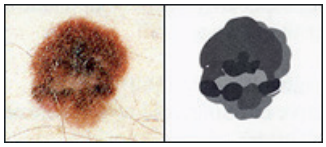
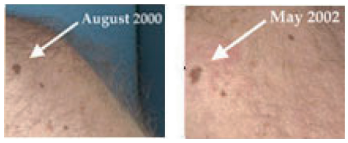
Describe findings/tattoos

Consultation No ☐ Yes ☐

Photos taken? No ☐ Yes ☐

Notes

Table A12.2. **ABCDE Scheme for orientating skin examination**

A. Asymmetry	If one half is not identical to the other half, suspect melanoma.	
B. Border irregularity	Notched, scalloped, ragged or poorly defined borders should lead us to suspect melanoma.	
C. Colour	Naevi usually have a uniform colour; if there is colour variability from black-brown to red-blue grey or white, suspect melanoma.	
D. Diameter/Difference	If the diameter is > 6 mm, suspect melanoma. Small lesions with some of the previous characteristics should also lead us to suspect melanoma. If there are multiple lesions with a more or less regular aspect but among them there is one that has a very "ugly" aspect compared to the rest (ugly duckling sign), suspect melanoma.	
E. Evolution	If there has been an evolution or change in appearance of a lesion, suspect melanoma. Any change – in size, shape, colour, elevation or another trait, or any new symptom such as bleeding, itching or crusting – points to danger.	

Images: https://www.skincancer.org/skin-cancer-information/melanoma/melanoma-warning-signs-and-images/.

References

1. Friedman RJ, Rigel DS, Kopf AW. Early detection of malignant melanoma: The role of physician examination and self-examination of the skin. *CA Cancer J Clin* 1985;35(3):130-51.
2. Whited JD, Grichnik JM. The rational clinical examination. Does this patient have a mole or a melanoma? *JAMA* 1998;279(9):696-701.

Appendix 13. **Donor and organ information forms**

Appendix 13.1. Donor information form (Eurotransplant, English-language version)

Appendix 13.2. Organ information form of the Foedus project (Agence de la biomédecine, France, English-language version)

Appendix 13.3. Organ offer information form of Scandiatransplant

Appendix 13.4. Deceased Donor organ report form of Scandiatransplant

The forms shown in this appendix are used for donor characterisation as well as for data exchange between European countries when cross-border organ exchange is intended. Staff should prefer to store and exchange the data electronically and use the form only as backup.

13.1. Donor information form (Eurotransplant, English-language version)

The donor information form is used within the Eurotransplant area (Austria, Belgium, Croatia, Germany, Hungary, Luxembourg, Netherlands) for data exchange during organ offer by the allocation office according to the data provided by the organ procurement organisation. This form is modified in its design when used within the IT systems of the different states. The donor and organ characteristics described in this questionnaire are based on the considerations outlined in chapters 6 and 7.

EUROTRANSPLANT DONOR INFORMATION FORM

Registration date / time	ET donor nr	Region Center	ABO Rh	NHBD: Y / N	Date of birth	Age	Sex	Weight	Height
				Type: I / II / III / IV					
DSO identity nr			Bloodgroup remarks						

TT lab	HLAmethod	A	A	A	A	B	B	B	B	Bw	Bw	Cw	Cw
	DNA Serology												
material	date / time	DR	DR	DR	DR	DR	DR	DQ	DQ	DQ	DQ	Cw	Cw

Microbiology (* is mandatory) date: Other microbiology results:

HIV Ab *	HIV Ag	HBsAg*	HBsAb	HBcAb*	HCV Ab*	CMV IgM *	CMV IgG *	Lues (VDRL / TPHA)	Toxo. Ab	EBV	Sepsis	Meningitis

Remarks on microbiology

Organs	Repor-ted	Explant. by local team	Reason not reported (specify)	Reason for withdrawal (specify)	Preservation fluid used	Consent to research
Heart	Y / N	☐				Y / N
Left lung	Y / N	☐				Y / N
Right lung	Y / N	☐				Y / N
Liver	Y / N	☐				Y / N
Pancreas	Y / N	☐				Y / N
Left kidney	Y / N	☐				Y / N
Right kidney	Y / N	☐				Y / N
Intestine	Y / N	☐				Y / N

Donor information

Donor identity:	Permission given:
Country of citizenship:	**Register checked :**

Contact data

Donor hospital:	Hospital tel nr:
Contact person (DSO coord):	Contact tel nr:
Hospital department: ESP region:	Contact other (GSM) tel nr:
ET office coordinator:	Explantation planned on date / time:

General Clinical data

Cause of death:	
Brain death date / time:	
Admission date / time:	Admission on ICU date / time:
Mechanical ventilation since date / time:	Urine catheter since date / time:
Cardiac arrest:	Total duration of cardiac arrest:
Date / time of last reanimation:	Duration of last reanimation:
Number of times the donor was reanimated:	
Donor comments:	

F1.1.2 Donor information form 31-01-2014 Also available on: www.eurotransplant.org

EUROTRANSPLANT DONOR INFORMATION FORM

Donor center	ET donor nr	ABO Rh	Date of birth

Medical History			
Hypertension:	since:	Treated:	
Diabetes Mellitus Type:	since:	Treated:	
Alcohol Abuses:	since:	Intake:	
Smoking: since:	packyears:	IV Drug abuse: since:	
Malignant Tumor	since:	Treated:	
Comments / other known illnesses:		Medication before admission:	

Physical data			
Diuresis:	ml in last …… hours	Diuresis last hour:	ml

Clinical data	Date:	Date:	Date:
Temperature	°C	°C	°C
Heart Frequency	/min	/min	/min
Systolic Bloodpres.	mmHg	mmHg	mmHg
Diastolic Bloodpres.	mmHg	mmHg	mmHg
CVP	cm H2O/ mmHg	cm H2O/ mmHg	cm H2O/ mmHg
Clinical deviations	Date / time:	Date / time:	Date / time:
Highest art BP	min. mmHg	min. mmHG	min. mmHg
Duration of low BP	min	min	min

Medication	Date: Dose:	Date: Dose:	Date: Dose:
Adrenaline			
Noradrenaline			
Dopamine			
Dobutamine			
Other vasopressor			
Blood transfusions: last 24 hours:			
Plasma expanders: last 24 hours:	product:	product:	product:
Other bloodproducts	product:	product:	product:
Antibiotics:	therapeutic / profylactic	therapeutic / profylactic	therapeutic / profylactic
Antidiuretics:			
Other medication (last 24 hours):			

General Remarks

EUROTRANSPLANT DONOR INFORMATION FORM

Donor center	ET donor nr	ABO Rh	Date of birth

Laboratory Values (* is mandatory)

Date / time							Normal values	calc. →	Normal values
Hb *						mmol/l / g/dl	7.5-11 mmol/l	X 1.6	12-16 g/dl
Ht *						%	40-54 %	X 0.01	0.4-0.54
Leuco's *						x 10^9/l	4.0-11.0 x 10^9/l		
Platelets *						x 10^9/l	130-400 x 10^9/l		
Ery's						x 10^{12}/l	3.5-5.9 x 10^{12}/l		
Na^{+} *						mmol/l	135-147 mmol/l		
K^{+} *						mmol/l	3.5-5.0 mmol/l		
Ca^{2+}						mmol/l	2.2-2.55 mmol/l		
Cl^{-}						mmol/l	95-105 mmol/l		
Glucose *						mmol/l / mg/dl	3.9-6.1 mmol/l	x 17.9	70-110mg/dl
Creatinine *						mmol/l / mg/dl	62-132 mmol/l	x 0.011	0.7-1.5mg/dl
Urea *						mmol/l / mg/dl	3 – 9 mmol/l	x 6	18-54 mg/dl
LDH *						U/l	50-240 U/l	x 0.016	0.8-3.8µkat/l
CPK *						U/l	0-150 U/l	x 0.016	0-2.5 µkat/l
CKMB *						U/l	<5 U/l <10%cpk	x 0.016	<0.08 µkat/l
Troponine						µg/l	< 0,1 µg/l		
ASAT / SGOT*						U/l	0-35 U/l	x 0.016	0-0.58 µkat/l
ALAT / SGPT*						U/l	0-35 U/l	x 0.016	0-0.58 µkat/l
γGT *						U/l	0-30 U/l	x 0.016	0-0.50 µkat/l
Bilirubin tot. *						µmol/l / mg/dl	3.4-20.4 µmol/l	x 0.058	0.2-1.2 mg/dl
Bilirubin dir. *						µmol/l / mg/dl	0-4 µmol/l	x 0.058	0-0.2 mg/dl
Alk. Phos. *						U/l	40-130 U/l	x 0.016	0.64-2.1µkat/l
Amylase *						U/l	0-130 U/l	x 0.016	0-2.17 µkat/l
Lipase						U/l	0-160 U/l	x 0.016	0-2.66 µkat/l
HBa1C						%	4-6 %		
Tot. Protein						g/l	60-80 g/l	x 0.10	6-8 g/dl
Albumin						g/l	25-60 g/l		60-65%
Fibrinogen						g/l / mg/dl	1.5-3.5 g/l	x 100	150-350 mg/dl
Quick / PT *						% / sec	70-100 %		10-13 sec
INR *							0.9-1.1		
APTT *						sec	26-34 sec		
AT III						%	70-120 %		
CRP*						mg/l	< 8 mg/l	x 0.10	< 0.8 mg/dl

Bloodgas and Ventilation

Date / time								Normal values	Normal values
FiO_2 (%) *						100 %	For 10 minutes		
PEEP *						+5 CM H_2O			
pH *								7.35-7.45	
pO_2 *							mmHg / kPa	80-100mmHg	9.5-13.5 kPa
pCO_2 *							mmHg / kPa	35-45mmHg	4.6-6.0 kPa
HCO_3 *							mmol/l	21-25mmol/l	
BE *							mmol/l		
O_2 sat. *							%	96-100%	

EUROTRANSPLANT DONOR INFORMATION FORM

Donor center	ET donor nr	ABO Rh	Date of birth

Bacteriology		**Urinalysis**	date/time	date/time
Urine:	date:	**Glucose:**		
		Protein:		
Sputum / Tracheal:	date:	**Sediment:**		
		ery's:		
Blood:	date:	**leuco's**		
		cyl.:		
Other:	date:	**bact.:**		
		other:		
Remarks Bacteriology:		**Remarks Urinalysis:**		

Other Diagnostics (* is mandatory)

Chest X-Ray * date:

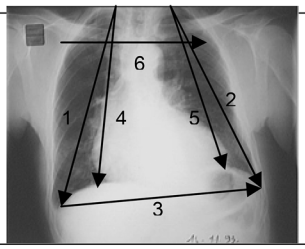
ECG * date:

Ultrasound heart date:

Bronchoscopy date:

Lung measurements	
1. Right apex to Right CPA	cm
2. Left apex to left CPA	cm
3. Right CPA to left CPA	cm
4. Right apex to diaphragma	cm
5. Left apex to diaphragma	cm
6. Thoraxwidth at lvl aortic arch	cm

Xray at 1m (end expiratory)
CPA is costo phrenic angle



Ultrasound abdomen * date:

Other diagnostics (ie. coronary angiography, CT Thorax, CT Abdomen:

13.2. Organ information form of the Foedus project (Agence de la biomédecine, France, English-language version)

This organ information form is used within the Foedus project to ensure safe and effective organ exchange across borders between different countries and their organ-exchange organisations. The donor and organ characteristics described in this questionnaire are based on the considerations outlined in chapters 6 and 7.

agence de la biomédecine

To be contacted:
Tel : **00 33 1 49 46 50 74**
Fax : 00 33 1 48 22 66 05
Email : **regulation.nationale@biomedecine.fr**

ORGAN(S) OFFER

Please advise within less than 1 hour whether you wish to accept this offer

Procurement/ Retrieval site: _____
Closest opened airport: _____

Heart *(coeur)* ☐	**Heart/Lungs** *(coeur –poumons)* ☐	**Small Bowel** ☐	**Pancreas** ☐
Lungs ☐	*Right Lung* ☐	*Left Lung* ☐	
Kidneys ☐	*Right Kidney* ☐	*Left Kidney* ☐	
Liver ☐	*Right lobe* ☐	*Left lobe* ☐	

Procurement/Retrieval time: : hrs *or planned* at : : hrs
Aortic cross clamp time: : hrs *on* DD/MM/YY
If DCD planned time for switch off: : *hrs*

DONOR:

Donor code/ ID: Type of Donor: DCD ☐ DBD…. ☐

ABO group O Rh+ ☐ Rh- ☐ *(Groupe sanguin)*	Age	Gender: ♂☐ ♀☐	Weight (kg) *(Poids)* *kg*	Height (cm) *(Taille)* *cm*
HLA	*A*	*B*	*DR*	*DQ*

Admission date in Hospital *(date d'admission)*: / /
Admission date in ICU *(date d'admission)*: / /

Ventilated from *(date de ventilation)*: / /

Cardiac arrest *(arrêt cardiaque)*: Yes ☐ / No ☐, No flow for min on / / ,

Immediate actions: External defibrillator *(choc électrique externe)* ☐

select drug if other => *specify:*

Date & Time of Death: / / & : hrs

Cause of Death : Select diagnosis

Chest: Yes ☐ No ☐ / Head: Yes ☐ No ☐ /Abdominal: Yes ☐ No ☐ /Other => specify: _____

If intoxication ☐ => select substance, if other => *specify:* _____

Other cause of death : ☐ => specify:_____

agence de la biomédecine

To be contacted:
Tel : **00 33 1 49 46 50 74**
Fax : 00 33 1 48 22 66 05
Email : **regulation.nationale@biomedecine.fr**

Past History:

Alcohol consumption (*Alcool*) : ☐/ quantity: since:

Stopped: ☐ since

Smoking status (*Fumeur*) : ☐/ quantity: since:

Stopped: ☐/since

Drug Abuse (*Drogues*) : ☐/ by IV: ☐/ Stopped: ☐/since comment *if any*:

Cardiovascular Disorders : ☐/, => ***Select type*** : ☐/ => specify: _____ Since :
DD/MM/YYYY & treatment : => specify:

Cancer : ☐ =>***Select*** : : Remission for more than 5 years : Yes ☐/ No ☐

Diabetes mellitus ☐/ & Type: ___

Chronic Infection : ☐/ => ***Select Chronic Infection*** Other ☐/ => specify: _____

Risk of pre-immunization : ☐/ => ***Select***

Other ☐/ => specify: _____

Previous Surgery *(Antécédants chirurgicaux)*: _____

Previous Treatment *(traitements antérieurs)*: _____

Clinical Data:

	: hrs *on*	: hrs *on*	: hrs *on*
Blood pressure : Average Haemodynamic unbalance : Yes ☐/ No ☐ /	mmHg	mmHg	mmHg
Heart rate	beats/ min	beats/ min	beats/ min
Diuresis	ml/h	ml/h	ml/h

Blood transfusion =>Last 24 h: Yes ☐/ No ☐

Current infections : ☐ select data Antibiotics => Last 24 h:Yes ☐ No ☐; if yes =>

_____

agence de la biomédecine

To be contacted:
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Fax : 00 33 1 48 22 66 05
Email : **regulation.nationale@biomedecine.fr**

Laboratory Data:		*At admission on* : hrs *on*	*Latest on* : hrs *on*
Haemoglobin	g/dl		
White cell	count /mm^3 X10 g/l		
Platelets	count /mm^3 X10 g/l		
Haematocrit	%		
Fibrinogen	g/l		
INR ☐ or PT ☐ or TQ ☐	% seconds		
Lactate	mmol/l		
Amylases	mmol/l		
Other /specify:			

Biological test (Add a X)	*Negative*	*Positive*	*Indeterminate (unreliable result)*	*In Process*	*Not tested*
HIV AgP24					
HIV Ab					
HCV Ab					
HBs Ag					
HBs Ab					
HBc Ab					
HTLV: I & II Ab					
HCV Ab					
CMV Ab					
Syphilis:(TPHA/VDRL)					
EBV Ab					
Toxoplasma Ab					
Others : _____					

Medication:		: hrs *on*	: hrs *on*	: hrs *on*
Dopamine/ Dobutamine :	γ/kg/min µg/kg/min			
Adrenaline/ Noradrenaline:	mg/h µg/kg/min			
Antidiuretic hormone	µg			
Corticoids	mg			
Others: _____ => specify units				

agence de la biomédecine

To be contacted:
Tel : **00 33 1 49 46 50 74**
Fax : 00 33 1 48 22 66 05
Email : **regulation.nationale@biomedecine.fr**

Organs Characterisation:

LIVER		: hrs *on*	: hrs *on*
ASAT	UI/l		
ALAT	UI/l		
GGT	UI/l		
Alk. Phos.	UI/l		
LDH	UI/l		
Albumin	g/l		
Bilirubin	mg/l		

Echography / Ultrasounds Yes ☐ No ☐	Hepatic size *(fleche hépatique)*	138mm
	Abnormalities	Steatosis ☐ at %
		Biliary duct dilatation ☐
		Vena cava : Permeability defect ☐ Thrombosis ☐
		Other ☐ => specify

KIDNEY		: hrs *on*	: hrs *on*
Na+	mmol/l		
K+	mmol/l		
Urea	mmol/l		
Creatinine	µmol/l		
Proteinuria	g/l		

Echography / Ultrasounds Yes ☐ No ☐	**Right**	Size **cm** (*taille D*)	
		Abnormaliries	Cyst/Tumor: ☐ size **cm** Biopsy in process : ☐
			Atherosclerosis : ☐
			Thrombosis : ☐
			Signs of obstruction : ☐
			Other: ☐ => specify
	Left	Size **cm** (*taille G*)	
		Abnormaliries	Cyst/Tumor: ☐ size **cm** Biopsy in process : ☐
			Atherosclerosis : ☐
			Thrombosis : ☐
			Signs of obstruction : ☐
			Other ☐ => specify

agence de la biomédecine

To be contacted:
Tel : **00 33 1 49 46 50 74**
Fax : 00 33 1 48 22 66 05
Email : **regulation.nationale@biomedecine.fr**

LUNGS	: hrs *on*	: hrs *on*
FiO_2	%	%
pH		
$PaCO_2$ mmHg		
PaO_2 mmHg		
HCO^{3-} mmol/l		
PEEP mmHg		
O_2 sat	%	%

Chest X-Ray Yes ☐ No ☐	Thoracic perimeter **cm** Abdominal perimeter **cm** Sternal height **cm**	
	Abnormaliries	Effusion ☐ *(épanchement)*
		Atelectasis ☐
		Pneumonia ☐
		Cyst/Tumor: ☐ size **cm** Biopsy in process : ☐
		Broncoscopy ***Select***
		Adenopathy ☐
		Other ☐ => specify

HEART	: hrs *on*	: hrs *on*
CPK UI/l		
CKMB UI/l		
Troponin ng/ml		

Electrocardiogram Normal ☐ Abnormal ☐	If Abnormal why:	
Vascular pathology	Yes ☐/ No ☐ If YES specify:	
Echography/ Ultrasounds Yes ☐ No ☐	**Abnormaliries**	Aortic injury ☐
		Atheroma ☐
		Aortic dissection ☐
		Aortic/ Vascular shrinkage ☐
		Other ☐ => specify
LVEF *(fract° d'éjection)*	%	
And / or SF *(fract°raccourcissement)*	%	
Septum size **mm**		
Dilation Right	Yes ☐/ No ☐	
Left	Yes ☐/ No ☐	
Contractility	Normal ☐ Abnormal ☐	

Reason for non-acceptance in country of origin : ***Select reason***
(Raison du refus dans le pays d'origine)
if other *=> specify:*_____

FACILITATING EXCHANGE OF ORGANS DONATED IN EU MEMBER STATES

This form arises from the project FOEDUS (grant agreement 2012 21 01) which has received funding from the European Union, in the framework of the Health Programme. The sole responsibility lies with the author and the Executive Agency is

Co-funded by the Health Programme of the European Union

13.3. Organ offer information form of Scandiatransplant

This organ offer information form is used within Scandiatransplant to ensure safe and effective organ exchange across borders between different countries and their organ-exchange organisations. The donor and organ characteristics described in this questionnaire are based on the considerations outlined in chapters 6 and 7.

This is an organ offer for:

☐ **Kidney-R** ☐ **Liver** ☐ **Heart** ☐ **Intestine** **Donor N°:** _____

☐ **Kidney-L** ☐ **Liver-Domino** ☐ **Lung-R** ☐ **Heartbeating donor**

☐ **Pancreas** ☐ **Liver-Split** ☐ **Lung-L** ☐ **Non heartbeating donor**

Transplant Coord _____ **Mobile** + _____

Procurement center _____ Phone + _____

City (Hospital) _____ Fax + _____

Country _____ Distance from airport _____

Blood group _____ ☐ Pos ☐ Neg Weight _____ kg Height _____ cm

Age: _____ ☐ F ☐ M Time of death _____

Cause of death _____ Date of admission _____ Vent. since _____

Blood pressure _____ MAP: _____ Diuresis _____ Temperature _____

Hypotensiv period _____ Duration _____ Cardiac arrest _____ Duration _____

Medication _____ Inotropic drugs _____

Alcohol/drug abuse: _____ Smoker _____ Pack year _____

Medical history _____

_____

ECG	☐ Yes	☐ No	☐ N.D.			HLA:	A	
ECHO	☐ Yes	☐ No	☐ N.D.				B	
Coronary angiography	☐ Yes	☐ No	☐ N.D.				C	
Chest X-ray	☐ Yes	☐ No	☐ N.D.				DR	
							DQ	
CMV	☐ Pos	☐ Neg	☐ N.D.	FiO_2 %		FiO_2 %	**100% - 5 min**	
HIV	☐ Pos	☐ Neg	☐ N.D.	pH		pH		
HbsAg	☐ Pos	☐ Neg	☐ N.D.	PCO_2		PCO_2		
Anti HCV	☐ Pos	☐ Neg	☐ N.D.	PO_2		PO_2		
Anti Hbc	☐ Pos	☐ Neg	☐ N.D.	BE		BE		PEEP
Anti Hbs	☐ Pos	☐ Neg	☐ N.D.	Sat	100 %	Sat	%	CVP
Syfilis	☐ Pos	☐ Neg	☐ N.D.					

Creatinine		Alc phos		Na (Sodium)	
B-Glucose		GGT		K (Potassium)	
Amylase		PK-INR		CRP	
Bilirubin		TPK			
ASAT		Hb			
ALAT		CK-MB			

Start of operation is planned at _____ hours We need Your answer within _____ minutes

Explantation is already performed - Cross clamp at: _____ hours

Reason for refusal at centre of origin:

ROTA-list (**Heart**-within Sctp) 1. _____ 2. _____ 3. _____ 4. _____ 5. _____

ROTA-list (**Lungs**-within Sctp) 1. _____ 2. _____ 3. _____ 4. _____ 5. _____

ROTA-list (**Liver**-within Sctp) 1. _____ 2. _____ 3. _____ 4. _____ 5. _____

Date: _____ Time: _____ Transplant Coord: _____

Reference values

Analyse	Sweden	Norway	Helsinki	Denmark
Creatinine	F: < 90 µmol/L M: < 100 µmol/L	50-105 µmol/L	F: 50-90 µmol/L M: 60-100 µmol/L	50-105 µmol/L
B-Glucose	4-6 mmol/l	3,7-5,1 mmol/L	4,0-6,1 mmol/L	4,2-6,3 mmol/L
Pa-Amylase	0,40-2,0 µkat/L	10-65 U/L	25-120 U/L	25-120 U/L
Bilirubin	< 26 µmol/L	3-26 µmol/L	4-20 µmol/L	5-25 µmol/L
ASAT (SGOT)	F: < 0,61 µkatl/L M: < 0,76 µkatl/L	15-45 U/L	F: 15-35 U/L M: 16-45 U/L	15-35 U/L
ALAT (SGPT)	F: < 0,76 µkatl/L M: < 1,10 µkatl/L	10-70 U/L	F: < 35 U/L M: 5 < 50 U/L	10-70 U/L
Alc Phos	< 1,9 µkat/L	35-105 U/L	35-105 U/L	35-105 U/L
GGT	F: < 0,76-1,3 µkat/L M: < 1,4-2,0 µkat/L	10-115 U/L	F: < 40 U/L M: < 60 U/L	15-115 U/L
LD	< 4,0 µkat/L	105-255 U/L	105-235 U/L	105-205 U/L
PK-INR	< 1,2	0,8-1,2	0,7-1,2	0,9-1,1
Hb	F: 117-153 g/L M: 134-170 g/L	11,6-16,6 g/dl	F: 117-155 g/L M: 134-167 g/L	7-10 mmol/L
Trombocytes	F: 165-387 10^9/L M: 145-348 10^9/L	125-400 10^9/L	150-360 E^9/L	145-390 10^9/L
Leucocytes	3,5-8,8 10^9/L	4,0-11,0 10^9/L	3,4-8,2 E^9/L	3,5-8,8 10^9/L
Na-Sodium	137-145 mmol/L	135-148 mmol/L	137-145 mmol/L	134-144 mmol/L
K-Potassium	3,6-4,6 mmol/L	3,4-4,3 mmol/L	3,3-4,9 mmol/L	3,2-4,7 mmol/L
CK-MB	< 5 µg/L	< 12 U/L	0-7 µg/L	< 10 U/L
Troponine I **Troponine T**	< 0,03 µg/L ≤ 0,03 µg/L	< 0,12 µg/L	< 15 ng/L	< 0,10 µg/L
CRP	< 10 mg/L	< 10 mg/L	< 10 mg/L	< 10 mg/L

2009-11-17/ACC

13.4. Deceased donor organ report form of Scandiatransplant

This organ report form is used within Scandiatransplant to summarise organ procurement data characteristics as outlined in chapters 6, 7 and 11.

Corr: 2017-05-19

Organ Form - Deceased Donor

Date (ddmmyy): _____ Surgeons: _____

Donor Proc. Center: _____ Tx Coord: _____

Donor Hospital: _____ Phone: _____

Signature - Transpl. Coord. _____

THIS ORGAN FORM CONCERNS THE FOLLOWING ORGAN:

☐ Kidney Right ☐ Liver ☐ Pancreas ☐ Heart ☐ SL Right ☐ DL

☐ Kidney Left ☐ Liver Split ☐ Pa-Islets ☐ Heart-Lung ☐ SL Left ☐ Recond. L ☐ Intestine

DONOR:

Donor no: _____ Initials: _____ Date of birth: _____

Cause of death: _____ Time of death: _____

Local number: _____ Length: _____ Weight: _____

ABO (Rh): _____ ☐ Female ☐ Male ☐ DBD ☐ DCD

VIROLOGY:

CMV IgG:	☐ Pos	☐ Neg	☐ N.D.
HBsAg:	☐ Pos	☐ Neg	☐ N.D.
Anti-HBc	☐ Pos	☐ Neg	☐ N.D.
Anti-HBs	☐ Pos	☐ Neg	☐ N.D.
Anti-HCV:	☐ Pos	☐ Neg	☐ N.D.
Anti-HIV:	☐ Pos	☐ Neg	☐ N.D.
Toxo IgG	☐ Pos	☐ Neg	☐ N.D.
Syfilis:	☐ Pos	☐ Neg	☐ N.D.

DONOR OPERATION / PERFUSION:

Start donor op: _____ hours Heparin: _____ Solu-Medrol: _____

Start of perfusion: _____ hours Mannitol: _____ Other: _____

Perf. solution: Aorta: _____ _____ ml Back table: _____ ml

Porta: _____ _____ ml Back table: _____ ml

Heart: _____ _____ ml

Lung: _____ _____ ml

Perf in donor: Excellent Good Bad Into ice box: _____ hours

On back table: _____ hours Start of machine perf: _____ hours

GRADE OF LIVER STEATOSIS:

None		☐
Mild	(< 30%)	☐
Moderate	(30-60%)	☐
Severe	(> 60%)	☐
Visual:		☐
Biopsy:		☐

ANY SPECIFIC COMMENTS:

PERMISSION FOR RESEARCH: ☐ Yes ☐ No

Samples enclosed: ☐ Spleen ☐ Blood ☐ Iliac artery ☐ Iliac vein ☐ Sputum

RECIPIENT:

Scandia no: _____ Initials: _____ Date of birth: _____ Date of transplant: _____

Revascularisation: _____ hours Cold ischemia time: _____ hours

Appendix 14. **Donor examination by various means**

- 14.1. Donor examination by chest X-ray or alternative imaging (Eurotransplant, English-language version)
- 14.2. Donor examination by bronchoscopy (Eurotransplant, English-language version)
- 14.3. Donor examination by echocardiography (Eurotransplant, English-language version)
- 14.4. Donor examination by electrocardiogram (Eurotransplant, English-language version)
- 14.5. Donor examination by coronary angiography or alternative imaging (Eurotransplant, English-language version)
- 14.6. Donor examination by abdominal ultrasound or alternative imaging (Eurotransplant, English-language version)
- 14.7. Donor examination by standardised blood gas analysis with lung recruitment (Eurotransplant, English-language version)

14.1. Donor examination by chest X-ray or alternative imaging (Eurotransplant, English-language version)

X-Ray Chest

Date of examination	Date	Time	Identity (Id-#)		
Trachea in the middle	☐ yes ☐ no				
ET tube cranial to carina	☐ yes ☐ no				
	Clear: any changes or pathologies?		☐ no	☐ yes	☐ not assessable
	Rib fracture		☐ no	☐ yes	☐ not assessable
	Pneumothorax		☐ no	☐ yes	☐ not assessable
	Pleura effusion		☐ no	☐ yes	☐ not assessable
	Pleura thickening		☐ no	☐ yes	☐ not assessable
Left lung	Atelectasis		☐ no	☐ yes	☐ not assessable
	Infiltrates		☐ no	☐ yes	☐ not assessable
	Bronchial thickening		☐ no	☐ yes	☐ not assessable
	Space occupying lesion		☐ no	☐ yes	☐ not assessable
	Emphysema		☐ no	☐ yes	☐ not assessable
	Interstitial lung disease		☐ no	☐ yes	☐ not assessable
	Clear: any changes or pathologies?		☐ no	☐ yes	☐ not assessable
	Rib fracture		☐ no	☐ yes	☐ not assessable
	Pneumothorax		☐ no	☐ yes	☐ not assessable
	Pleura effusion		☐ no	☐ yes	☐ not assessable
	Pleura thickening		☐ no	☐ yes	☐ not assessable
Right lung	Atelectasis		☐ no	☐ yes	☐ not assessable
	Infiltrates		☐ no	☐ yes	☐ not assessable
	Bronchial thickening		☐ no	☐ yes	☐ not assessable
	Space occupying lesion		☐ no	☐ yes	☐ not assessable
	Emphysema		☐ no	☐ yes	☐ not assessable
	Interstitial lung disease		☐ no	☐ yes	☐ not assessable
Foreign body	☐ no ☐ left lung ☐ right lung ☐ both lungs ☐ trachea				☐ not assessable
Prominent Hilum	☐ no ☐ yes				☐ not assessable
Mediastinum enlarged	☐ no ☐ yes				☐ not assessable
Heart shadow enlarged	☐ no ☐ yes				☐ not assessable
Remark					
Examiner					

14.2. Donor examination by bronchoscopy (Eurotransplant, English-language version)

Bronchoscopy

Date of examination	Date	Time	Identity (Id-#)		
Trachea	Epithelium: any changes or pathologies	☐ no	☐ yes		☐not assessable
	Inflammation	☐ no	☐ yes		
	Bleeding	☐ no	☐ yes		
	Ulceration	☐ no	☐ yes		
	Tumour	☐ no	☐ yes		
	Aspiration	☐ no	☐ yes		
	Putrid secretion	☐ no	☐ yes		
	Amount, colour, consistency of secretions :				
	Additional bronchus	☐ no	☐ yes		
Bronchus left	Epithelium: any changes or pathologies?	☐ no	☐ yes		☐not assessable
	Inflammation	☐ no	☐ yes		
	Bleeding	☐ no	☐ yes		
	Ulceration	☐ no	☐ yes		
	Tumour	☐ no	☐ yes		
	Putrid secretion	☐ no	☐ yes		
	Localization of secretion in bronchus		☐ main b.	☐ lobar b.	☐ sublobar b.
	Secretion after suction	☐ clean	☐ refilling from peripheral		
	Aspiration	☐ no	☐ yes		
Bronchus right	Epithelium: any changes or pathologies?	☐ no	☐ yes		☐not assessable
	Inflammation	☐ no	☐ yes		
	Bleeding	☐ no	☐ yes		
	Ulceration	☐ no	☐ yes		
	Tumour	☐ no	☐ yes		
	Putrid secretion	☐ no	☐ yes		
	Localization of secretion in bronchus		☐ main b.	☐ lobar b.	☐ sublobar b.
	Secretion after suction	☐ clean	☐ refilling from peripheral		
	Aspiration	☐ no	☐ yes		
Remark (Bronchus):					
Tracheal / bronchial aspirate sent to microbiological laboratory		☐Yes	☐no		
BAL (bronchoalveolar lavage) sent to microbiological laboratory		☐Yes	☐no		
Examiner					

14.3. Donor examination by echocardiography (Eurotransplant, English-language version)

Echocardiography

Date of examination	Date	Time	Identity						
Type of examination	☐ TTE ☐ TEE		(Id-#)						
Visualisation	☐ normal ☐ limited ☐ severely limited								
Haemodynamic measurement at time of echocardiography									
MAP		mmHg	Inotropes at examination ☐ yes↓ ☐ no						
Heart rate		BPM	Kind and						
CVP		mmHg	Dosage						
Left heart									
If case of measurement not possible please describe qualitative	LA		mm (≤59)						
	LV-EDD		mm (≤59)	LV-PWd		mm (≤10)	IVSd		mm (≤10)
	LV-ESD		mm (≤38)	LV-PWs		mm	IVSs		mm
	LV-EF		% ☐ Simpson (≥55) ☐ Teichholz ☐ estimated				or LV-FS		% (≥25)
	LVH Hypertrophy	☐ normal	☐ moderate	☐ severe					☐ not assessable
	LVF Function systolic	☐ normal	☐ mildly reduced	☐ moderately reduced		☐ severely reduced			☐ not assessable
	LV Function diastolic*	☐ normal	☐ abnormal relaxation	☐ pseudo normalisation		☐ restrictive filling			☐ not assessable
		☐ none	☐ regional akinesia↓		☐ hypokinesia↓				☐ not assessable
LV-regional wall motion disorder (please specify)									
Right Heart									
If case of measurement not possible please describe qualitative	RV-EDD		mm (<35)	RV-TAPSE		mm (>15)			
	RV-ESD		mm (<25)	RV-Wand		mm (≤5)			
				RA		mm (≤45)			
	RV function	☐ normal	☐ function reduced						☐ not assessable
	RV size	☐ normal	☐ hypertrophy						☐ not assessable
	RV morphology	☐ normal	☐ moderate dilated		☐ dilated				☐ not assessable
Aorta and Valves									
Aorta	Aortic-Annulus		mm (<28)	Aorta-ascendens		mm(<30)	☐ not assessable		
	Morphology								
Aortic valve	Insufficiency	☐ none	☐ 1	☐ 2	☐ 3	☐ not assessable			
	Stenosis	☐ none	☐ mild	☐ moderate	☐ severe	☐ not assessable			
	Morphology	☐ normal	☐ thickened	☐ calcification		☐ not assessable			
Mitral valve	Insufficiency	☐ none	☐ 1	☐ 2	☐ 3	☐ not assessable			
	Stenosis	☐ none	☐ mild	☐ moderate	☐ severe	☐ not assessable			
	Anterior leaflet	☐ normal	☐ thickened	☐ calcification		☐ not assessable			
	Posterior leaflet	☐ normal	☐ thickened	☐ calcification		☐ not assessable			
Pulmonary valve	Insufficiency	☐ none	☐ 1	☐ 2	☐ 3	☐ not assessable			
	Stenosis	☐ none	☐ mild	☐ moderate	☐ severe	☐ not assessable			
	Morphology	☐ normal	☐ thickened	☐ calcification		☐ not assessable			
Tricuspid valve	Insufficiency	☐ none	☐ 1	☐ 2	☐ 3	☐ not assessable			
	Stenosis	☐ none	☐ mild	☐ moderate	☐ severe	☐ not assessable			
	Morphology	☐ normal	☐ thickened	☐ calcification		☐ not assessable			
Pericardial effusion	☐ no	☐ yes	Thickness		mm	☐ not assessable			
Further measurements, remarks (e.g. suspicion of endocarditis, malformation (ASD / VSD))									
Examiner									

***LFV diastolic only when LVF systolic normal**

14.4. Donor examination by electrocardiogram (Eurotransplant, English-language version)

ECG (Electrocardiogram)

Date of examination	Date	Time	Identity	
ECG plot at ET	☐ no ☐ yes		(Id-#)	
Heart rate (BPM)				
Sinus-Rhythm (SR)	☐ SR (yes) ☐ absent (no)			☐ not assessable
AV-Block	☐ none ☐ present (yes)			☐ not assessable
Atrial arrhythmia	☐ none ☐ present (yes)			☐ not assessable
Ventricular arrhythmia	☐ none ☐ present (yes)			☐ not assessable
QRS-changes	☐ none ☐ left bundle bloc ☐ bifsc. bloc ☐ Infarct like ☐ right bundle bloc ☐ other ☐ not assessable			
remark				
ST-T-Segment changes	☐ none ☐ present (yes)			☐ not assessable
remark				
LV-hypertrophy	☐ none ☐ present (yes)		☐ not assessable	
QTc-time	☐ normal ☐ prolonged (yes) (QTc time in ms: ☐ ☐ not assessable			
Remark				
Examiner				

14.5. Donor examination by coronary angiography or alternative imaging (Eurotransplant, English-language version)

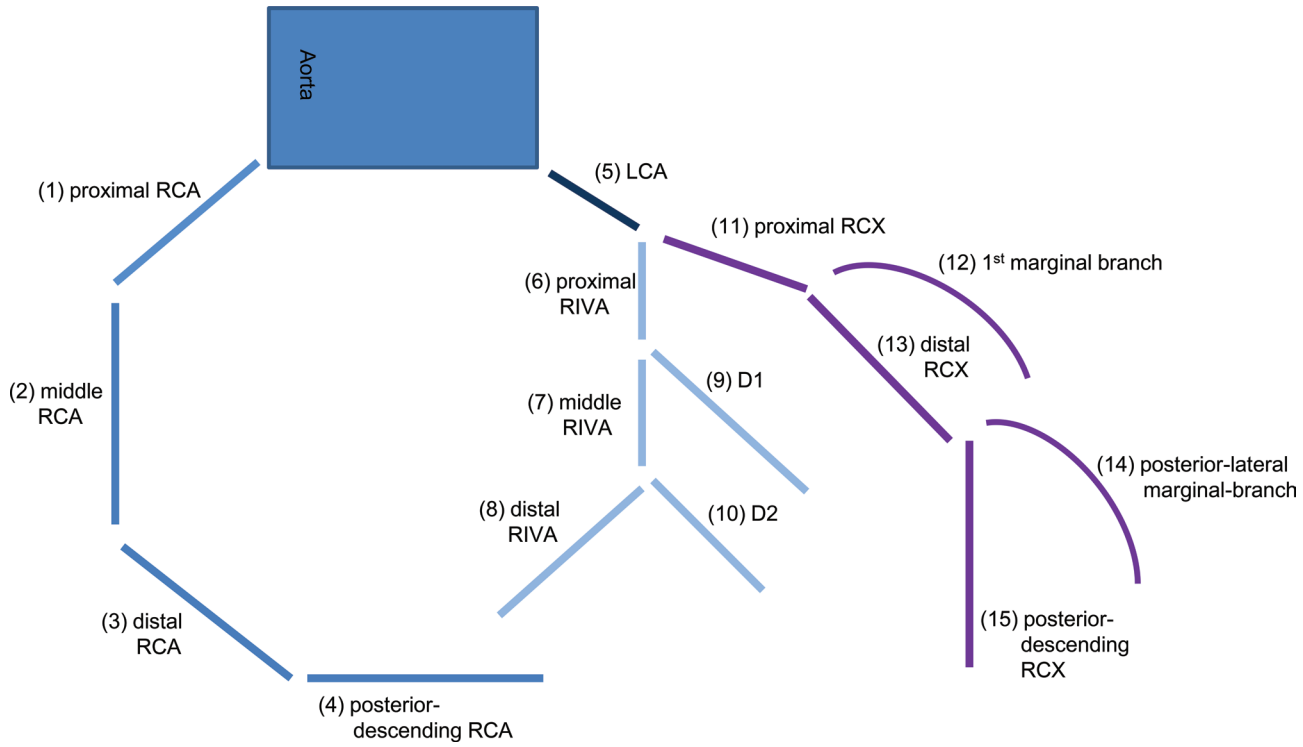
Coronary angiography

Date of examination	Date	Time	Identity (Id-#)	

	Degree of stenosis (in % or luminal irregularities (LIR))							
Vessel	none	LIR-25%	26-50%	51-75%	76-99%	100%	not existent	not assessable
RCA and branches	☐	☐	☐	☐	☐	☐	☐	☐
↳proximal RCA (1)	☐	☐	☐	☐	☐	☐	☐	☐
↳middle RCA (2)	☐	☐	☐	☐	☐	☐	☐	☐
↳distal RCA (3)	☐	☐	☐	☐	☐	☐	☐	☐
↳post.-descend. RCA (4)	☐	☐	☐	☐	☐	☐	☐	☐
↳ **Type of stenosis**		☐ LIR	☐ A concentric <1cm		☐ B eccentric 1-2cm		☐ C diffuse > 2cm	
	none	LIR-25%	26-50%	51-75%	76-99%	100%	not existent	not assessable
LM/LCA- (5)	☐	☐	☐	☐	☐	☐	☐	☐
	none	LIR-25%	26-50%	51-75%	76-99%	100%	not existent	not assessable
LAD/RIVA and branches	☐	☐	☐	☐	☐	☐	☐	☐
↳proximal RIVA/LAD (6)	☐	☐	☐	☐	☐	☐	☐	☐
↳middle RIVA/LAD (7)	☐	☐	☐	☐	☐	☐	☐	☐
↳distal RIVA/LAD (8)	☐	☐	☐	☐	☐	☐	☐	☐
↳1st diagonal branch/D1 (9)	☐	☐	☐	☐	☐	☐	☐	☐
↳2nd diagonal branch /D2 (10)	☐	☐	☐	☐	☐	☐	☐	☐
↳ **Type of stenosis**		☐ LIR	☐ A concentric <1cm		☐ B eccentric 1-2cm		☐ C diffuse > 2cm	
	none	LIR-25%	26-50%	51-75%	76-99%	100%	not existent	not assessable
RCX/LCX and branches	☐	☐	☐	☐	☐	☐	☐	☐
↳proximal RCX/LCX (11)	☐	☐	☐	☐	☐	☐	☐	☐
↳1st marginal branch/OM (12)	☐	☐	☐	☐	☐	☐	☐	☐
↳distal RCX/LCX (13)	☐	☐	☐	☐	☐	☐	☐	☐
↳posterolat. marginal/PL (14)	☐	☐	☐	☐	☐	☐	☐	☐
↳post.-descend. RCX/PD (15)	☐	☐	☐	☐	☐	☐	☐	☐
↳ **Type of stenosis**		☐ LIR	☐ A concentric <1cm		☐ B eccentric 1-2cm		☐ C diffuse > 2cm	

Major supply	☐ right ☐ left ☐ not assessable
Vessel variant	☐ normal ☐ variant
Levocardiography↓	☐ no ☐ yes (not necessary in case of good echocardiography assessment)
Other measurement	
Remark:	
Examiner	

☐ In case of complex findings use drawing provided at opposite



The rationale and indication for this investigation is outlined in Section 7.2.5. The pathway of standardised examination corresponds to Figure 7.5 and Table 7.6. For further convenience the design of the form can be adapted to national requirements as long as the contents remain identical in order to assure electronic data exchange.

14.6. Donor examination by abdominal ultrasound or alternative imaging (Eurotransplant, English-language version)

Sonography -Abdomen

Date of examination	Date Time			Identity (ID-Nr.)	
Liver	Parenchyma	☐ normal	☐ slightly hyper-echogenous	☐ severely hyper-echogenous ☐ cirrhosis	☐ n.a.
	Diameter MCL (cm)		if MCL not measured size: ☐ normal	☐ small ☐ large ☐ enlarged	☐ n.a.
	space occupying lesion	☐ no	☐ yes, localisation in segment		☐ n.a.
			Possibly ☐ tumour ☐ abscess ☐ angioma ☐ contusion ☐ haematoma ☐ cyst ☐ ??		
			Specify		
	liver edge	☐ sharp	☐ blunt		☐ n.a.
	bile duct Intrahepatic	☐ normal	☐ dilated		☐ n.a.
	bile duct Extrahepatic	☐ normal	☐ dilated ☐ Choledocholithiasis		☐ n.a.
	Portal vein	☐ free	☐ thrombosis		☐ n.a.
	Vena cava	☐ normal	☐ yes ☐ volume depleted ☐ volume overload		☐ n.a.
	remarks				
Gall bladder		☐ normal	☐ cholecystolithiasis ☐ cholecystitis ☐ cholecystectomy ☐ other pathologies		☐ n.a.
	space occupying lesion	☐ no	☐ yes		☐ n.a.
			Possibly ☐ tumour ☐ abscess ☐ cyst ☐ ??		
			Specify		
Pan-creas	Parenchyma	☐ normal	☐ lipomatosis ☐ edema ☐ fibrosis ☐ other		☐ n.a.
	Calcification	☐ no	☐ yes		☐ n.a.
	Pancreatitis	☐ no	☐ yes		☐ n.a.
	space occupying lesion	☐ no	☐ yes, localisation: ☐ head ☐ corpus ☐ tail ☐ multiple		☐ n.a.
			Possibly ☐ tumour ☐ abscess ☐ angioma ☐ contusion ☐ haematoma ☐ cyst ☐ ??		
			Specify		
	remarks				
Spleen	Size	☐ normal	☐ splenomegaly ☐ haematoma ☐ liquid fringe ☐ multiple		☐ n.a.
			splenomegaly (cm)	haematoma (cm)	liquid fringe (cm)
	Remarks				
Kidney left	Longitudinal diameter (cm)		Short diameter (cm)	Mass of renal cortex (cm)	
	Parenchyma	☐ normal	☐ reduced- atrophic ☐ atrophic ☐ nephrectomy ☐ other pathologies		☐ n.a.
	renal calculi	☐ none	☐ yes (Nephrolithiasis)		☐ n.a.
	signs of obstruction	☐ none	☐ yes		☐ n.a.
	space occupying lesion	☐ no	☐ yes, localisation: ☐ upper pole ☐ middle ☐ lower pole ☐ multiple		☐ n.a.
			Possibly ☐ tumour ☐ abscess ☐ angioma ☐ contusion ☐ haematoma ☐ cyst ☐ ??		
			Specify		
	remarks				
Kidney right	Longitudinal diameter (cm)		Short diameter (cm)	Mass of renal cortex (cm)	
	Parenchyma	☐ normal	☐ reduced- atrophic ☐ atrophic ☐ nephrectomy ☐ other pathologies		☐ n.a.
	Renal calculi	☐ none	☐ yes (Nephrolithiasis)		☐ n.a.
	Signs of obstruction	☐ none	☐ yes		☐ n.a.
	space occupying lesion	☐ no	☐ yes, localisation: ☐ upper pole ☐ middle ☐ lower pole ☐ multiple		☐ n. a.
			Possibly ☐ tumour ☐ abscess ☐ angioma ☐ contusion ☐ haematoma ☐ cyst ☐ ??		
			Specify		
	remarks				
Free liquid / ascites		☐ none	☐ minimal ☐ significant		☐ n.a.
	amount / distribution				
Aorta		☐ normal	☐ single plaques ☐ severe arteriosclerosis ☐ aneurysm ☐ stenosis		☐ n.a.
	diameter (cm)		morphology		
Paraaortic lymphoma		☐ none	☐ yes	if yes size lymphoma (cm)	☐ n.a.
	remarks				
Small pelvis		☐ normal	☐ pathological		☐ n.a.
Prostate		☐ normal	☐ enlarged ☐ pathological		☐ n.a.
Urinary bladder		☐ normal	☐ pathological		☐ n.a.
Remarks					
Examiner					

Possibly =Possible explanation of space occupying lesion; n.a.=not assessable.

14.7. Donor examination by standardised blood gas analysis with lung recruitment (Eurotransplant, English-language version)

Standardized bloodgas evaluation at FIO2=1.0 after lung recruitment

Date of examination	Datum	Uhrzeit	Identity (D.-Nr.)			
Suction of secretion performed			☐ yes	☐ no	☐ not possible	
Lung recruitment (back squeezing performed)			☐ yes	☐ no	☐ not possible	
Sample drawn after at FIO_2=1.0 for 10 min.			☐ yes	☐ no	☐ not possible	
PEEP (cmH_2O)						
pH						
paO_2 (mmHg temperature corrected)*				or paO_2 (kPA temperature corrected)*		
$paCO_2$ (mmHg temperature corrected)*				or $paCO_2$ (kPA temperature corrected)*		
HCO_3^- (mmol/l temperature corrected)						
Base-Excess (mmol/l temperature corrected)						
examiner						

***mmHg * 0,1333224 = kPA; kPA * 7,5006150504 = mmHg**

Appendix 15. **Grading for biopsies at histopathological examinations (English-language version)**

This table summarises a proposed lexicon of standard terms which can be used when investigating biopsies of livers, or other samples, during donor characterisation or at procurement. The preferred concept is to use a standardised list of values instead of free text because this will allow correlation of clinical data with findings of histopathological examination. Further exchange of samples and images of samples or technology of telemedicine should be used to compare data between investigating institutions and second-opinion experts as well as donor and recipient centres.

Field label	**List of values**	**Item needed**	
date of specimen	dd.mm.yyyy hh:mm	liver	other
specimen from	• brain • heart • lung left • lung right • lymph node (localisation sampling point) • liver • pancreas • spleen • stomach • intestine (localisation see sampling point) • kidney left • kidney right • urinary bladder • prostate • ovary • other (localisation see sampling point)	liver	other
sampling point/additional information/indication/ leading question/clinical data	free text to describe localisation	liver	other
localisation of specimen	• localised lesion • representative for whole organ • other (please specify)	liver	other
specimen ID (laboratory)	free text	liver	other
specimen incoming (date/time)	***dd.mm.yyyy hh:mm***	***liver***	***other***
macroscopic aspect of specimen	free text	liver	other

Field label	List of values	Item needed	
kind of specimen/biopsy	• sub-capsular wedge biopsy (liver) • wedge-biopsy • biopsy histology • core biopsy (via skin puncture) • other	liver	other
kind of investigation	• frozen section • final report (after formalin fixation and paraffin embedded) • other	liver	other
macrovesicular steatosis (% of parenchyma as integral of the parenchymal surface examined)	• none (0-5 %) • 5-10 % • 11-20 % • 21-30 % • 31-40 % • 41-50 % • 51-60 % • > 60 % • not assessable	liver	
additional lipid staining	• no • yes	liver	
fibrosis	• none • slight (portal) fibrosis • portal fibrosis with early stages of septum formation • fibrosis with septa formation and changes of liver architecture • cirrhosis • not assessable	liver	
microvesicular steatosis (not relevant for use of liver for transplantation)*	• none (or slight) • moderate • severe • not assessable	liver	
steatohepatitis*	• none or slight inflammation (no steatohepatitis) • moderate inflammation (steatohepatitis) • severe inflammation (steatohepatitis) • not assessable	liver	
inflammatory changes of portal fields*	• none or mild portal inflammation • moderate portal inflammation • severe portal inflammation with periportal spread into parenchyma • not assessable	liver	
inflammatory changes of parenchyma*	• none or slight inflammation • moderate acinar inflammation • severe acinar inflammation • not assessable	liver	
cholangitis*	• none • chronic (see comment for specification) • florid (see comment for specification) • not assessable	liver	
necrosis*	• none or insignificant • necrosis (see comment for specification) • not assessable	liver	
cholestasis*	• none • cholestasis (see comment for specification) • not assessable	liver	
neoplasia/malignancy	• no evidence for neoplasia in specimen • benign neoplasia (see comment for specification) • malignancy (see comment for specification) • uncertain dignity (see comment for specification)	liver	other
comment/further results/additional findings	free text to describe or explain any other relevant finding (e.g. malignancy) as well as to mention other pathologies (e.g. pigmentations in liver biopsy)	liver	other

Field label	List of values	Item needed	
consult investigating pathologist for medical issues	free text for comment by investigating pathologist	liver	other
→ at phone number	free text	liver	other

* facultative fields which should be considered according to the indication for investigation.

Appendix 16. **Hepatitis C – direct-acting antiviral drugs (HCV-DAA)**

Thorough understanding of the Hepatitis C virus (HCV) structure and replication has led to the development of the direct-acting antiviral drugs (DAA). These drugs are small molecules that target non-structural (NS) viral proteins and inhibit HCV replication. The introduction of these agents has changed the treatment of patients with HCV infection, with sustained virological response (SVR) being achieved in over 95 % of patients [1-3]. Note that grafts procured from HCV-viraemic donors can be used in HCV-non-viraemic recipients, when proper treatment pathway and protocol are in place; these include approved access to drugs and informed patient consent [2-3].

Pan-genotypic or genotype-specific drug combinations can be used (see Table A) [2]. Drug dosage adjustments based on renal and liver function, previous exposure to anti-viral drugs and drug interactions have to be taken into account [2-4]. Treatment experts and up-to-date guidelines must be consulted.

From the point of view of the donation process, determination of the donor's HCV genotype or viral load is not necessary.

Table A. Summary of recommended pan-genotypic and genotype-specific DAA combinations

Genotype / DAA combination	1a	1b	2	3	4	5	6
sofosbuvir + velpatasvir	c/a/tx	c/a/tx	c/a/tx	[c]/a/tx	c/a/tx	c/a/tx	c/a/tx
sofosbuvir + velpatasvir + voxilaprevir				c			
glecaprevir + pibrentasvir	c/a/tx	c/a/tx	c/a/tx	c/a/tx	c/a/tx	c/a/tx	c/a/tx
sofosbuvir + ledipasvir	c/a/tx	c/a/tx			c/a/tx	c/a/tx	c/a/tx
paritaprevir + ombitasvir + ritonavir + dasabuvir		c					
grazoprevir + elbasvir	c	c/a			c/a		

These are the DAA combinations recommended by the clinical practice guideline of the European Association for the Study of the Liver in 2018 [2]. The specific safety advice must be checked regarding the intended use of a particular combination in a patient.

tx = combination can be used after non-hepatic organ transplantation.

a = combination can be used in case of acute hepatitis C.

c = combination can be used in case of chronic hepatitis C.

References

1. Hézode C. Pan-genotypic treatment regimens for hepatitis C virus: advantages and disadvantages in high- and low-income regions. *J Viral Hepat* 2017;24(2):92-101. https://doi.org/10.1111/jvh.12635.

2. European Association for the Study of the Liver. EASL recommendations on treatment of hepatitis C 2018. *J Hepatol* 2018;69(2):461-511, updated version (2020) available at www.easl.eu/research/our-contributions/clinical-practice-guidelines, last accessed 10 August 2021.
3. American Association for the Study of Liver Diseases and the Infectious Diseases Society of America. HCV guidance: recommendations for testing, managing, and treating Hepatitis C. American Association for the Study of Liver Diseases and the Infectious Diseases Society of America, 2019, available at www.hcvguidelines.org, last accessed 10 August 2021.
4. University of Liverpool. HEP drug interactions: interaction checker, available at www.hep-druginteractions.org, accessed 10 August 2021.

Appendix 17. **Checklist for Covid-19 infection used in risk assessment of organ donors (United Kingdom)**

FRM6439/4 – COVID-19 SNOD Checklist

NHS
Blood and Transplant
Effective date: 08/07/2020

Please complete this checklist as per guidance

- **Questions 1 - 12 are in relation to the potential donor**
- Question 13 is in relation to other patients on the ICU
- Question 14 - please complete if required

Donation should only proceed where there is NO suspicion of COVID-19. In relation to COVID-19 the full medical and clinical history should be considered alongside virology results. To help you in assessing the safety of transplantation and as part of donor characterisation, please consider the points below:

	Question	Comments/Details
1	Name, DOB, Donor ID, Unit Name	
2	Date and reason for admission to hospital	
3	Date and time of admission to ICU	
4	Location on admission and subsequent movement in ICU (i.e. side room, open bay)	
5	Chest X Ray/CT **Please ensure the chest X ray/CT is reviewed by the ICU medical team.** Any abnormalities to the chest X ray/CT? Yes/ No (please give details)	Chest X Ray/CT details:
6	Have there been changes in the chest X-Ray image? Yes/No (please give details)	

FRM6439/4 – COVID-19 SNOD Checklist

NHS
Blood and Transplant
Effective date: 08/07/2020

7	Any history/previous diagnosis of COVID-19?		
Symptom		**Yes/No**	**Date of onset of symptoms**
Fever?			
New, continuous cough?			
Loss of / change in taste or smell?			
Other?			
8	In relation to Q7, was COVID-19 confirmed? Yes/No?	Date of Diagnosis:	
9	Did this result in a hospital admission? Yes/No?	Date of hospital admission:	
10	Any exposure to a proven or suspect case of COVID-19 in the last 14 days? (please give details)		
11	**Please confirm the ITU team feel COVID has been reasonably excluded. (history, exam, tests, radiology)** **Yes/ No**		

Accepting Centres - If further detail is required for risk assessment, please contact the SNOD.

12	Admission testing details:				
Sample Type		**Indication for testing**	**Date taken**	**Time taken**	**Result***

***Failure of internal control amplification invalidates the test – no result available (system failure). The test needs to be repeated on the same or another sample. This is not an indeterminate result.**
N.B. Some patients cannot have nose swab taken (i.e. extensive trauma or bleeding); very rarely, neither nose or throat swab can be obtained so an oral swab can be taken instead.

If the patient has any symptoms or is suspected to have COVID-19 then donation should NOT proceed

FRM6439/4 – COVID-19 SNOD Checklist

NHS
Blood and Transplant
Effective date: 08/07/2020

Please Respect the Confidentiality of All Other Patients – Do NOT record Patient ID Details

If there are any other patients COVID 19 positive, suspicion of COVID 19 or patients undergoing surveillance for COVID19, please answer the questions below:

13	**COVID 19 positive patients** Please advise if: Donor in single room COVID-19 patients are cohorted or within separate side of ICU with cohorted staff Are there other patients on the ICU who are COVID positive or suspected that are relevant to the potential donor (Consider Infection, Prevention and Control measures) Include information such as any concerns or identified risks, date of admission and testing undertaken.	
14	Any other relevant information:	

Completed By
Name:

Specialist Nurse Organ Donation (SNOD)

Appendix 18. **Reporting form for rare diseases and intoxication (France, English-language version)**

agence de la biomédecine

RECORD SHEET:
CANCER – INFECTION – POISONING – RARE DISEASE
Click here to enter a date.

Area	**Donor N°** Click here to enter text.	**ICD-10***

DONOR: selected/not selected DONOR: organ removed/ organ not removed

CAUSE (*if answer is negative*): Click here to enter text.

PATHOLOGY, PROGRESSION AND TREATMENT, BRIEF DESCRIPTION

CANCER[1] ☐ INFECTION ☐ POISONING ☐ RARE DISEASE ☐ OTHER[2] ☐

[1] ***if cancer:***
History of the disease (mandatory):
- active cancer at the time of collection NO ☐ YES ☐
- donor's history of "cured" cancer NO ☐ YES ☐
- family history of cancer NO ☐ YES ☐

System: Click here to enter text. Organ (mandatory): Click here to enter text.
Histological type: Click here to enter text. Extent of invasion: Click here to enter text.
Date of diagnosis: Click here to enter text.
Treatments: Click here to enter text.

[2] ***if other,*** *specify the condition (e.g. morbid obesity, allergy, polydipsia leading to water intoxication, etc…):* Click here to enter text.

Description: **Click here to enter text.**

EXPERT CONSULTED NO ☐ YES ☐ Speciality: Click here to enter text.

Expert's opinion: Click here to enter text.

ORGANS removed (☒)	**H** ☐	**H-L** ☐	**RL LL DL** ☐ ☐ ☐	**TL RL LL** ☐ ☐ ☐	**RK LK DK** ☐ ☐ ☐	**Pa** ☐	**In** ☐
Not removed owing to the disease?	?	?	? ? ?	? ? ?	? ? ?	?	?
Transplanted (Y/N)	?	?	? ? ?	? ? ?	? ? ?	?	?
Not transplanted owing to the disease?	?	?	? ? ?	? ? ?	? ? ?	?	?
Anat. path. (AP) Transf. (Valves) Destruc. (DST)	?	?	? ? ?	? ? ?	? ? ?	?.	?.
Recipient No.	?	?	? ? ?	? ? ?	? ? ?	?.	?.

Appendix 19. **Antibiotic prophylaxis in deceased organ donors**

Summary of findings

No prospective studies were identified that investigated the role of routine antibiotic prophylaxis in deceased donors on transplant rates or post-transplant recipient outcomes. One retrospective study, comparing pefloxacine prophylaxis to a historical control cohort without, demonstrated a reduction in perfusion fluid contamination and recipient infection with prophylaxis.

General prophylaxis in ITU patients has been shown in metanalyses of large numbers of RCTs to be beneficial for patient outcomes (risk of respiratory infection and overall mortality), so it is likely that many donors will have received some antibiotic therapy during their admission. In keeping with the data from the overall ITU population, positive cultures on BAL are common in potential donors, which may have implications for potential lung donors in particular. Use of antibiotics with a narrow Gram-negative spectrum have been associated with increased risk of multidrug-resistant organisms.

Clinical question

'Does the use of antibiotic prophylaxis in potential deceased organ donors improve organ recovery or post-transplant outcomes?'

PICOS

Population: Adult patients (aged 18 or over) admitted to an ITU with the diagnosis of death by neurological criteria, being considered as a potential organ donor.

Intervention: Administration of prophylactic antibiotics on the ICU.

Comparator: No antibiotics, placebo or alternative therapy (including alternative antibiotic therapies).

Outcomes: Primary outcome was the number of organs transplanted by donor. Secondary outcomes include proportion of potential donors proceeding to donation, graft function, incidence of surgical site infection or donor-derived post-transplant infection.

Study design: Systematic reviews, randomised controlled trials or prospective or retrospective cohort studies.

Search strategy and results

The Transplant Library (TL) was searched from inception to 21 May 2020. The TL includes all randomised controlled trials and systematic reviews in the field of solid organ transplantation published as full text or in abstract form, sourced from MEDLINE, EMBASE and the Cochrane Library.

The search strategy used is as follows:

1. exp TISSUE DONORS/
2. (donor* or donat$).ti,ab.
3. or/1-2
4. exp ANTIBIOTIC PROPHYLAXIS/
5. exp INFECTION CONTROL/
6. (Anti-Infective Agents/ or Anti-Bacterial Agents/ or beta-Lactamase Inhibitors/ or Anti-Infective Agents, Urinary/ or antibiotic.ab,ti. or antibiotics.ab,ti. or anti-biotic.ab,ti. or anti-biotics.ab,ti. or anti-bacterial.ab,ti. or antibacterial.ab,ti. or bacteriocidal.

ab,ti. or bacteriocide.ab,ti. or bacteriocides. ab,ti. or Antiinfective.ab,ti. or Anti-infective. ab,ti. or antiseptic.ab,ti. or antiseptics.ab,ti. or anti-septic.ab,ti. or anti-septics.ab,ti. or antimicrobial.ab,ti. or anti-microbial. ab,ti. or microbicide.ab,ti. or microbicides. ab,ti. or infection*.ab,ti. or biapenem.ab,ti. or brobactam.ab,ti. or carbapenem.ab,ti. or clavulanate potassium.ab,ti. or clavulanic acid. ab,ti. or doripenem.ab,ti. or ertapenem.ab,ti. or fropenem.ab,ti. or imipenem.ab,ti. or l 786392. ab,ti. or lenapenem.ab,ti. or meropenem. ab,ti. or monobactam.ab,ti. or nacubactam. ab,ti. or nocardicin.ab,ti. or nocardicinic acid. ab,ti. or panipenem.ab,ti. or pirazmonam. ab,ti. or razupenem.ab,ti. or ritipenem. ab,ti. or sanfetrinem.ab,ti. or sulbactam. ab,ti. or sulopenem.ab,ti. or sultamicillin. ab,ti. or tazobactam.ab,ti. or tebipenem. ab,ti. or thienamycin.ab,ti. or timentin.ab,ti. or tomopenem.ab,ti. or tribactam.ab,ti. or trinem derivative.ab,ti. or u 78608.ab,ti. or benzathine cefalexin.ab,ti. or benzathine cefapirin.ab,ti. or carbacephem.ab,ti. or cefacetrile.ab,ti. or cefaclor.ab,ti. or cefadroxil. ab,ti. or cefalexin.ab,ti. or cefaloglycin.ab,ti. or cefaloram.ab,ti. or cefaloridine.ab,ti. or cefalotin.ab,ti. or cefamandole.ab,ti. or cefapirin.ab,ti. or cefatrizine.ab,ti. or cefazaflur. ab,ti. or cefazedone.ab,ti. or cefazolin. ab,ti. or cefbuperazone.ab,ti. or cefcanel. ab,ti. or cefcapene.ab,ti. or cefclidin.ab,ti. or cefdaloxime.ab,ti. or cefdinir.ab,ti. or cefditoren. ab,ti. or cefepime.ab,ti. or cefetamet.ab,ti. or cefetecol.ab,ti. or cefiderocol.ab,ti. or cefixime. ab,ti. or cefluprenam.ab,ti. or cefmatilen.ab,ti. or cefmenoxime.ab,ti. or cefmetazole.ab,ti. or cefminox.ab,ti. or cefodizime.ab,ti. or cefonicid. ab,ti. or cefoperazone.ab,ti. or ceforanide. ab,ti. or cefoselis.ab,ti. or cefotaxime.ab,ti. or cefotetan.ab,ti. or cefotiam.ab,ti. or cefovecin. ab,ti. or cefoxitin.ab,ti. or cefozopran.ab,ti. or cefpimizole.ab,ti. or cefpiramide.ab,ti. or cefpirome.ab,ti. or cefpodoxime.ab,ti. or cefprozil.ab,ti. or cefquinome.ab,ti. or cefradine. ab,ti. or cefroxadine.ab,ti. or cefsulodin.ab,ti. or ceftaroline.ab,ti. or ceftazidime.ab,ti. or cefteram.ab,ti. or ceftezole.ab,ti. or ceftibuten. ab,ti. or ceftiofur.ab,ti. or ceftizoxime.ab,ti. or ceftobiprole.ab,ti. or ceftolozane.ab,ti. or ceftriaxone.ab,ti. or cefuroxime.ab,ti. or cefuzonam.ab,ti. or cephalosporin*.ab,ti. or cephamycin.ab,ti. or deacetoxycephalosporin C.ab,ti. or deacetylcefotaxime.ab,ti. or deacetylcephalosporin C.ab,ti. or fleroxacin deacetylcefotaxime ester.ab,ti. or flomoxef. ab,ti. or latamoxef.ab,ti. or loracarbef.ab,ti. or nitrocefin.ab,ti. or thiophenoxycefalotin. ab,ti. or aztreonam.ab,ti. or carumonam. ab,ti. or gloximonam.ab,ti. or sulfazecin. ab,ti. or tigemonam.ab,ti. or adicillin.ab,ti. or almecillin.ab,ti. or aminopenicillin. ab,ti. or amoxicillin.ab,ti. or ampicillin. ab,ti. or apalcillin.ab,ti. or aspoxicillin.ab,ti. or azidocillin.ab,ti. or azlocillin.ab,ti. or bacampicillin.ab,ti. or bacmecillinam.ab,ti. or carbenicillin.ab,ti. or carfecillin.ab,ti. or carindacillin.ab,ti. or cloxacillin.ab,ti. or cyclacillin.ab,ti. or dicloxacillin.ab,ti. or epicillin.ab,ti. or flucloxacillin.ab,ti. or flumoxil. ab,ti. or fomidacillin.ab,ti. or furbenicillin. ab,ti. or fuzlocillin.ab,ti. or hetacillin.ab,ti. or isopenicillin N.ab,ti. or lenampicillin.ab,ti. or mecillinam.ab,ti. or metampicillin.ab,ti. or meticillin.ab,ti. or mezlocillin.ab,ti. or miraxid.ab,ti. or nafcillin.ab,ti. or optocillin. ab,ti. or oxacillin.ab,ti. or penamecillin. ab,ti. or penethamate.ab,ti. or penicillic acid. ab,ti. or penicillin.ab,ti. or penicilloic acid. ab,ti. or pheneticillin.ab,ti. or piperacillin. ab,ti. or pivampicillin.ab,ti. or pivmecillinam. ab,ti. or propicillin.ab,ti. or quinacillin.ab,ti. or retacillin.ab,ti. or sulbenicillin.ab,ti. or talampicillin.ab,ti. or tameticillin.ab,ti. or temocillin.ab,ti. or ticarcillin.ab,ti. or tobicillin. ab,ti. or triplopen.ab,ti. or ureidopenicillin. ab,ti. or avibactam.ab,ti. or brobactam.ab,ti. or clavulanic acid.ab,ti. or nacubactam. ab,ti. or relebactam.ab,ti. or sulbactam. ab,ti. or tazobactam.ab,ti. or timentin.ab,ti. or vaborbactam.ab,ti. or zidebactam.ab,ti. or albomycin.ab,ti. or Amdinocillin.ab,ti. or amifloxacin.ab,ti. or Amikacin.ab,ti. or antofloxacin.ab,ti. or Apramycin.ab,ti. or Avilamycin.ab,ti. or Azithromycin.ab,ti. or Bacitracin.ab,ti. or Bacteriocins.ab,ti. or Balofloxacin.ab,ti. or bekanamycin.ab,ti. or benzathinebenzylpenicillin.ab,ti. orbenzathine cloxacillin.ab,ti. or benzofuroquinolinium. ab,ti. or beta-Lactams.ab,ti. or Cephaloridine. ab,ti. or Cephacetrile.ab,ti. or Cephalexin. ab,ti. or Cephaloglycin.ab,ti. or Cephalothin. ab,ti. or Cephapirin.ab,ti. or Cephradine.ab,ti. or Cethromycin.ab,ti. or Chlortetracycline. ab,ti. or Cilastatin.ab,ti. or Ciprofloxacin.ab,ti. or Clarithromycin.ab,ti. or Clinafloxacin. ab,ti. or Clindamycin.ab,ti. or Clofazimine. ab,ti. or Colistin.ab,ti. or Daptomycin.ab,ti.

or Dibekacin.ab,ti. or Doxycycline.ab,ti. or Edeine.ab,ti. or Enoxacin.ab,ti. or Enrofloxacin.ab,ti. or Erythromycin.ab,ti. or Finafloxacin.ab,ti. or Floxacillin.ab,ti. or Fluoroquinolone*.ab,ti. or Fosfomycin.ab,ti. or Fosmidomycin.ab,ti. or Gemifloxacin.ab,ti. or Grepafloxaci.ab,ti. or Lactam*.ab,ti. or Levofloxacin.ab,ti. or Lincosamide*.ab,ti. or Lomefloxacin.ab,ti. or Marbofloxacin.ab,ti. or Methampicillin.ab,ti. or Methicillin.ab,ti. or Meropenem.ab,ti. or Moxalactam.ab,ti. or Moxifloxacin.ab,ti. or Mupirocin.ab,ti. or Nadifloxacin.ab,ti. or Nitrofurantoin.ab,ti. or Norfloxacin.ab,ti. or Nystatin.ab,ti. or Ofloxacin.ab,ti. or Oleandomycin.ab,ti. or Pefloxacin.ab,ti. or Penicillanic.ab,ti. or Penicillin*.ab,ti. or Pipemidic Acid.ab,ti. or Prulifloxacin.ab,ti. or Sparfloxacin.ab,ti. or Staphylococcin.ab,ti. or Sulfacetamide.ab,ti. or Sulfadiazine.ab,ti. or Sulfaguanol.ab,ti. or Sulfamerazine.ab,ti. or Sulfameter.ab,ti. or Sulfamethoxypyridazine.ab,ti. or Sulfanilamide.ab,ti. or Syringomycin.ab,ti. or Tedizolid.ab,ti. or Teicoplanin.ab,ti. or Temafloxacin.ab,ti. or Tetarimycin.ab,ti. or Tetracenomycin.ab,ti. or Tetracycline.ab,ti. or Tigecycline.ab,ti. or Tobramycin.ab,ti. or Tomaymycin.ab,ti. or Trimethoprim.ab,ti. or Sulfamethoxazole.ab,ti. or Ulifloxacin.ab,ti. or Vancomycin.ab,ti. or doxorubicin.ab,ti. or adriamycin.ab,ti. or rufloxacin.ab,ti.) adj3 ("prevention and control".fs. or premedication/ or prevent*.ab,ti. or premedication.ab,ti. or premedications.ab,ti. or prophyla*.ab,ti.)
7. or/4-6
8. exp ANIMALS/ not HUMANS/
9. 7 not 8

Searches identified 150 potentially relevant references. Of these, no RCTs or systematic reviews matched the PICOS defined above.

Searches were therefore expanded to include non-randomised studies. We searched MEDLINE and EMBASE from inception to 21/05/2020. In order to create a manageable search set, the free-text donor criteria (2) above were refined to:

2. ((organ or renal or kidney or liver or lung or heart or cardiac or cardiothoracic) adj3 (donor* or donat$)).ti,ab.

This search yielded 2 436 potentially relevant references. None of these studies met the full PICO criteria defined above. However, a small number of studies that may have some relevance to the question are outlined below.

Systematic reviews

No systematic reviews were identified that met the inclusion criteria. However, the following study may be of interest:

Liberati *et al.* (2009). Antibiotic prophylaxis to reduce respiratory tract infections and mortality in adults receiving intensive care. *Cochrane Database Syst Rev.* 2009(4):CD000022.

This Cochrane review metanalyses RCTs investigating the use of antibiotic prophylaxis in patients admitted to intensive care units. Use of antibiotics is associated with a reduction in risk of respiratory tract infections (OR 0.28, 95 % CI 0.20-0.38) and overall mortality (OR 0.75, 95 % CI 0.65-0.87). However, few of the included studies investigate the impact of routine prophylaxis on risk of antibiotic resistance. These results relate to the outcomes of general ITU patients, rather than potential donors.

Randomised controlled trials

No randomised controlled trials were identified that met the inclusion criteria.

Cohort studies

One retrospective cohort study was identified that meets the inclusion criteria defined above:

Pacholczyk *et al.* (1996). Bacterial infections transmitted from the donor: antibiotic prophylaxis in the donor. *Transplantation Proceedings* 28(1): 184-5.

This old study describes a change in practice, with a switch from no antibiotic prophylaxis to a single dose of pefloxacine in cadaveric kidney donors. The authors provide the rates of positive perfusion fluid cultures, recipient infection and donor-attributable infection before and after the change, but do not present a statistical comparison. Positive perfusion fluid cultures were seen in 26.9 % cases prior to antibiotic use, and 12.7 % after. Recipient infectious complications were 60.9 % before and 33.3 % after, and donor-transmitted infections were 7.2 % before and 3 % after. Given the retrospective nature of the control cohort, it is possible that other changes in practice contributed towards the fall in infection rates.

The following studies do not meet the full inclusion criteria, but may be of interest:

Anesi *et al.* (2019). Risk factors for multidrug-resistant organisms among deceased organ donors. *American Journal of Transplantation* 19(9): 2468-78.

This retrospective multi-centre analysis investigated risk factors for multi-drug resistant organisms (MDRO) in deceased organ donors. Exposure to antibiotics with a narrow Gram-negative spectrum independently increased the risk of MDRO in the donor (HR 1.13, 95 % CI 1.00-1.27, p = 0.045), and the risk increased with duration. Overall antibiotic exposure was not a risk factor. No post-transplant outcomes are reported, hence the study does not meet the inclusion criteria outlined above.

Corbel *et al.* (2020). Microbiological epidemiology of preservation fluids in transplanted kidney: a nationwide retrospective observational study. *Clinical Microbiology & Infection* 26(4): 475-84.

This retrospective national study from France investigated risk factors for positive kidney perfusion fluids. Although it included both living and deceased donor transplants, over 80 % were deceased. Donor antibiotic therapy was associated with a lower risk of positive perfusion fluid cultures (OR 0.6, 95 % CI 0.5-0.7). No other post-transplant outcomes are reported.

Shafaghi *et al.* (2011). Microbial pattern of bronchoalveolar lavage in brain dead donors. *Transplantation Proceedings* 43(2): 422-3.

This prospective study in 80 DBD donors investigated the incidence of positive BAL in potential lung donors. A high proportion of donors (38 %) had positive BAL cultures, leading the authors to conclude that antibiotic prophylaxis for donors may be warranted. However, the study did not investigate the impact of donor antibiotic prophylaxis directly.

Zenati *et al.* (1990). Influence of the donor lung on development of early infections in lung transplant recipients. *Journal of Heart Transplantation* 9(5): 502-8.

This small study investigated the culture results of tracheas from lung donors, relating them to clinical outcomes in recipients. Other than candida, early infections in recipients were generally with organisms different to those seen in the donor trachea, and antibiotic prophylaxis in the donor was not found to be a significant risk factor for infection in the recipient.

Appendix 20. *En bloc* liver–pancreas removal in deceased brain-dead donors

Summary of findings

Only two studies, including a cohort study and a case series, were identified on *en bloc* liver and pancreas removal. However, neither of the two studies defined their donor population as '> 18 years' and 'brain dead'. They also did not report outcomes related to time for the organs to reach cold storage temperature (4 °C). Hence, they did not fully meet the inclusion criteria.
A few comparative cohort studies and case-series that reported on simultaneous liver and pancreas procurement were identified. Although the method of organ procurement in these studies was not described as '*en bloc*', they were still included in this report and have been marked as 'studies that may be of interest'. Studies that reported on multiple organ procurement from the same donors in addition to pancreas and liver (e.g. heart, kidneys etc.) were excluded.
In general, simultaneous liver and pancreas removal did not seem to have detrimental effects in transplant outcomes after either liver or pancreas transplantation. Despite the absence of data on statistical significance for survival outcomes, in most of the included cohort studies, allograft survival appeared to be slightly better in transplant patients receiving grafts from combined liver–pancreas donors compared to pancreas-only or liver-only donors. Studies that did report the test of significance, however, found that the differences in the survival outcomes between the two groups were not significant.

Clinical question

'Does *en bloc* retrieval of liver and pancreas lead to better transplant outcomes compared to procurement of liver and pancreas separately?'

PICOS

Population: Adult patients over the age of 18 who proceed to donation after brain death and donate liver and pancreas.
Intervention: *En bloc* removal of liver and pancreas.
Comparator: Separate removal of liver and pancreas.
Outcomes: The primary outcome was the time to reaching cold storage temperature (4 °C) for the organs. The secondary outcomes were transplant outcomes and complications.
Study design: Systematic reviews, randomised controlled trials (RCTs), comparative cohort studies (retrospective or prospective) or case series.

Search strategy and results

The Transplant Library (TL) was searched from inception to 19 August 2020. The TL includes all RCTs and systematic reviews in the field of solid organ transplantation published as full text or in abstract form, sourced mainly from MEDLINE/PubMed and hand-searches of congress proceedings.

The search strategy used is as follows:

1. exp liver/
2. exp pancreas/
3. 1 and 2
4. (liver-pancreas or pancreas-liver or ((liver$ or hepatic$) and pancrea$)).ti,ab.
5. 3 or 4
6. (en-bloc$ or en bloc$ or combin$ or simultaneous$).ti,ab.

7. (retriev* or remov* or preserv* or procur* or transplant*).ti,ab.
8. 5 and 6 and 7
9. animals/
10. 8 not 9
11. limit 10 to english language

The search retrieved 6 potentially relevant references. None of the systematic reviews or RCTs identified matched the PICOS criteria defined above.

Therefore, MEDLINE Ovid was searched from inception to 19/08/20. The search yielded a total of 734 references. None of these studies fully met the pre-defined PICO criteria. However, a small number of studies that are outlined below may have some relevance to the research question.

Systematic reviews

No systematic reviews were identified.

Randomised controlled trials

No randomised controlled trials were identified.

Comparative cohort studies

Only one cohort study was identified on *en bloc* liver and pancreas procurement:

Imagawa *et al.* (1996). Rapid en bloc technique for pancreas-liver procurement. Improved early liver function. *Transplantation* 61(11): 1605-9.

This study compares the functional outcomes of pancreas and liver transplants procured from 32 combined liver–pancreas donors and 15 age-matched patients receiving grafts from liver-only donors. Of the 32 simultaneous liver–pancreas donors, 15 were obtained using the rapid *en bloc* method and 17 were procured using the *in situ* technique. The mean (± standard error) donor ages were 34 ± 3.2 years, 30 ± 3.4 years and 33 ± 4.8 years for the *in situ*, *en bloc* and liver-only groups respectively. All pancreas retrieved using the *en bloc* technique had immediate function with no evidence of graft pancreatitis. For liver transplant recipients, the 1-year actuarial graft survival rate was 71 % for the *in situ* group, 87 % for the *en bloc* group and 100 % for the liver-only group, while 1-year patient survival rate was 76 %, 87 %, and 100 % respectively for these three groups. The statistical significance for the survival outcomes was not reported. The *en bloc* and liver-only groups showed significantly lower early liver graft function compared to the *in situ* group.

Although the following studies report on simultaneous retrieval of liver and pancreas without the use of an *en bloc* technique, they might be of interest:

Dunn *et al.* (1991). Evidence that combined procurement of pancreas and liver grafts does not affect transplant outcome. *Transplantation* 51(1): 150-7.

This study compares the functional outcomes of liver and pancreas transplants retrieved from simultaneous liver–pancreas donors to those when only the liver or the pancreas was retrieved; 64 grafts were procured from simultaneous liver–pancreas donors, whereas 101 pancreas and 62 livers were procured from non-liver and non-pancreas donors respectively. No statistical differences were observed in the technical failure rate, the overall 1-year graft survival or the 1-year actuarial patient survival in pancreas transplant recipients from the combined liver–pancreas donor group compared to the non-liver donor group. Similar results were seen with regard to survival outcomes, technical failure rate and primary nonfunction rate of liver transplant patients receiving grafts from combined liver–pancreas donors *versus* non-pancreas donors. The authors thus concluded that simultaneous retrieval of liver and pancreas grafts had no significant detrimental effects in transplant outcomes after either liver or pancreas transplantation.

Illner *et al.* (1992). Pancreatic graft outcome after combined whole pancreas and liver retrieval. *Transplantation Proceedings* 24(3): 821.

This small study compares transplant outcomes of 26 pancreas transplant recipients divided into two groups: group I, consisting of 11 patients that received pancreatic grafts from pancreas-only donors; and group II, with 15 patients receiving pancreas from simultaneous pancreas–liver donors. The 1-year pancreatic graft function rate was higher in group II (67 %) than group 1 (45 %). Both groups had similar early endocrine function. Patients in group II were also reported to have slightly lower nonimmunological pancreatic graft failure rate. However, the authors did not report data on statistical significance for any of the outcomes.

Kim *et al.* (1996). Combined procurement of liver and pancreas does not influence early graft function and survival. *Transplantation Proceedings* 28(3): 1882-4.

This retrospective study compares the outcomes of pancreas and liver transplants procured

from 6 combined liver–pancreas donors, 5 non-liver donors and 12 non-pancreas donors. There were no cases of vascular thrombosis in pancreas grafts obtained from combined liver–pancreas donors, whereas 1 case of vascular thrombosis was observed in the pancreas allograft obtained from the non-liver donor group. The actuarial patient survival at 1 month following pancreas transplantation was 100 % in both the groups. The pancreatic graft survival at 1 month post-transplant was 100 % in the combined retrieval group and 66.7 % in the isolated pancreas retrieval group. No cases of initial nonfunction were seen in the two groups. Of the 12 liver grafts transplanted from the isolated liver retrieval group, there was 1 case of initial nonfunction and no case of vascular thrombosis. The liver grafts procured from the combined liver-pancreas group had one case of vascular thrombosis and no cases of initial nonfunction at 1 month post-transplant. The actuarial patient survival at 1 month after liver transplant was 83.3 % in both combined retrieval group and the isolated liver retrieval group, whereas the liver graft survival at 1 month of follow-up was 83.3 % and 75.0 % in the two groups respectively. The study did not report data on the test of significance for the survival outcomes.

Morel *et al.* (1991). Effect of simultaneous liver retrieval, retrieval team, and preservation time on cadaver whole-organ, bladder-drained pancreatic allograft survival rates. *Transplantation Proceedings* 23(1 Pt 2): 1640-2.

This study reports transplant outcomes for pancreas allografts procured from 93 simultaneous liver–pancreas donors and 97 non-liver donors. The overall pancreas graft survival rates for the combined procurement group and the pancreas-only procurement group were 87 % and 86 % at 1 month of follow-up, and 61 % and 55 % at 1 year of follow-up, respectively. The combined retrieval group had 5 cases of pancreas graft thrombosis and 1 case of primary nonfunction, whereas the pancreas-only retrieval group had 8 cases of thrombosis and 2 cases of primary nonfunction.

Sansalone *et al.* (1994). Right hepatic artery replacement from superior mesenteric artery in combined liver-whole pancreas procurement. Technical problems and liver graft artery reconstruction. *Transplantation Proceedings* 26(6): 3537-9.

This study compares the outcomes of liver transplants obtained from 14 combined liver–pancreas donors and 78 liver-only donors, with mean (± standard deviation) ages of 25 ± 4 years and 31 ± 11 years respectively. The simultaneous liver–pancreas group showed a lower incidence of acute rejection (21.4 % *v.* 24.4 %) and chronic rejection (0 % *v.* 3.8 %) but a higher rate of major infection (35.7 % *v.* 34.6 %) compared to the liver-only group. The tests of significance for the outcomes were not reported by the study.

Sanseverino *et al.* (1991). Technique of pancreas revascularization after combined liver and pancreas harvesting in the same cadaveric donor. *Clinical Transplantation* 5(1): 55-9.

This is another cohort study comparing the transplantation outcomes of pancreatic grafts procured from 62 combined liver–pancreas donors (group I) and 104 non-liver donors (group II). In group I, the percentage of functioning grafts was 51.6 %, the rejection rate was 11.2 %, and the arterial and venous thrombosis rates were 13 % and 18 % respectively. Whereas in group II, the percentage of functioning grafts was 29.8 %, the rejection rate was 27.8 % and the arterial and venous thrombosis rates were 5.7 % and 15.3 % respectively. No significant differences were observed between the two groups. The authors suggested that the lower rate of rejection and better allograft survival observed in group I could be attributed to improvements in immunosuppressive protocols with time.

Schlumpf *et al.* (1990). Combined procurement of pancreas and liver grafts does not affect transplant outcome. *Transplantation Proceedings* 22(4): 2074-5.

In this study, the authors compare the transplant outcomes of pancreas and liver grafts obtained from 64 simultaneous liver-pancreas donors and 102 non-liver donors. The combined liver–pancreas procurement group had 1-month and 1-year pancreas graft survival rates of 83 % and 61 % respectively, and a technical failure rate of 20 %. The pancreas graft recipients from the non-liver group had 1-month and 1-year graft survival rates of 83 % and 49 % respectively, and a technical failure rate of 25 %. The differences in the graft survival rates between the two donor groups were not significant. The 1-year liver graft function rate was 72 %. The authors concluded that the combined retrieval of liver and pancreas did not have any detrimental effects on the transplant outcomes of either organ.

Case series

Only one case series was identified on *en bloc* liver and pancreas procurement:

Pinna *et al.* (1997). Rapid *en bloc* technique for liver and pancreas procurement. *Transplantation Proceedings* 29(1-2): 647-8.

This study evaluated the clinical outcomes of pancreas and liver transplants obtained from 56 simultaneous liver–pancreas donors, 55 of which were transplanted. The liver and pancreas allografts were harvested using a rapid *en bloc* technique. The mean (± standard deviation) donor age was 25 ± 5 years. Of the liver transplants, 53 functioned immediately, one arrested immediately following reperfusion and one needed retransplantation at 3 days post-transplant due to primary nonfunction. Among the pancreas transplant recipients, 9 of them experienced graft loss, 4 of which were suspected to be caused by donor related factors and the remaining 5 due to reasons unrelated to the donor.

The following studies report on simultaneous retrieval of liver and pancreas without the use of an *en bloc* technique. However, they might be of interest:

Johnson *et al.* (1990). Simultaneous liver and pancreas procurement—a simplified method. *Transplantation Proceedings* 22(2): 425-6.

This is a case series involving six simultaneous liver and pancreas procurements and their subsequent transplantation. Each of the 12 transplants showed immediate function. In pancreas transplant recipients, blood glucose levels were immediately normalised and urinary amylase progressively rose to > 10 000 U/L by the third day post-transplant in all patients. Bile output was immediate and synthetic function was adequate in the recipients of liver transplant. Neither of the two groups experienced any technical or preservation related complications.

Mayes and Schulak (1990). Pancreas revascularization following combined liver and pancreas procurement. *Transplantation Proceedings* 22(2): 588-9.

This case series reports on transplant outcomes following procurement of 9 simultaneous liver and pancreas allografts. Combined pancreas–kidney transplant was performed in all pancreas transplant cases. Pancreatic function at 1 month was categorised as good in 7 patients, while the remaining 2 experienced thrombosis. Similarly, 7 patients in the liver transplant group also had good liver function at 1 month follow-up, whereas the remaining 2 died of haemorrhage or rejection. The authors suggested that these losses were likely to be technically-related rather than procurement-related.

Appendix 21. *Ante mortem* heparin in DCD donors

Summary of findings

There is limited evidence regarding the outcome of *ante mortem* administration of heparin. No randomised controlled trials have been conducted. The most convincing evidence comes from registry analyses of US data that demonstrate that heparin administration is not associated with the organ discard rate in DCD kidneys and livers. DCD kidneys that received *ante mortem* heparin showed similar clinical outcomes as DCD kidneys that did not receive *ante mortem* heparin; however, DCD livers that did not receive heparin showed an increased risk of graft failure and primary non-function compared to DCD livers that did receive *ante mortem* heparin.

Clinical question

'Does the administration of ante-mortem heparin improve transplant rates and clinical outcomes in recipients of donation after circulatory death (DCD) grafts?'

PICOS

Population: This study will include adult patients over the age of 18 who proceed to donation following circulatory arrest.

Intervention: Administration of *ante mortem* heparin.

Comparator: No heparin administration.

Outcomes: The primary outcomes will be the number of organs transplanted from each donor. The secondary outcomes will be transplant outcomes and complications as well as risks for donor.

Study design: Reviews, randomised controlled trials or prospective or retrospective cohort studies.

Search strategy and results

The Transplant Library (TL) was searched from inception to 25 August 2020. The TL includes all randomised controlled trials and selected systematic reviews in the field of solid organ transplantation published as full text or in abstract form, sourced mainly from MEDLINE/PubMed and hand-searches of congress proceedings.

The search strategy used is as follows:

1. heparin

Searches identified 24 potentially relevant references. One systematic review met the inclusion criteria defined above.

Systematic reviews

Cao *et al.* (2016). Donation after circulatory death for liver transplantation: a meta-analysis on the location of life support withdrawal affecting outcomes. *Transplantation* 100(7):1513-24.

PubMed link: https://pubmed.ncbi.nlm.nih.gov/27014794/

Commentary on the meta-analysis:

Kramer and Doig (2016). Premortem heparin administration and location of withdrawal of life-sustaining interventions in DCD: lack of high-quality evidence precludes definitive conclusions. *Transplantation* 100(10):e102-3.

PubMed link: https://pubmed.ncbi.nlm.nih.gov/27482963/

A secondary aim of this meta-analysis was to review the effect of *ante mortem* heparin on outcomes in DCD liver transplantation. The review included 23 studies reporting on 1 184 DCD liver recipients. An exploratory analysis found that the *ante mortem* heparin administration reduced the odds of primary non-function from 11.24 (2 studies, 95 % CI 1.99-63.37; P = 0.006) to 3.48 (5 studies 95 % CI 1.79-6.76; P < 0.001).

The following systematic review may also be of interest:

Shahrestani *et al.* (2017). Outcomes from pancreatic transplantation in donation after cardiac death: a systematic review and meta-analysis. *Transplantation* 101(1):122-30.

PubMed link: https://pubmed.ncbi.nlm.nih.gov/26950713/

The systematic review and meta-analysis aimed to describe donor approaches and recipient outcomes from DCD pancreas transplantation. Where possible, clinical outcomes were compared between DCD and DBD pancreas transplants. Eighteen studies were included reporting on data from 643 DCD pancreas transplant recipients. Three of 18 studies reported *ante mortem* heparin administration. An exploratory subgroup analysis of two studies that used *ante mortem* heparin found no difference in the incidence of thrombosis between DCD and DBD pancreases (Odds ratio (OR) 1.29; 95 % CI, 0.47-3.55; P = 0.62). Another subgroup analysis of two studies that did not use *ante mortem* heparin showed that there may be a lower incidence in thrombosis in DBD pancreases *versus* DCD pancreases (OR, 1.94; 95 % CI, 0.99-3.82; P = 0.05). The authors suggest that they there may be a role for *ante mortem* heparin in reducing thrombosis rates in DCD pancreases.

Searches were expanded to include non-randomised studies. We searched MEDLINE and EMBASE from inception to 25 August 2020 using the search strategy below.

1. (cardiac or non heart-beating or circulatory or nonheartbeating or non-heartbeating or nhb$ or dcd).ti,ab.
2. heparin/ or heparin.ti,ab.
3. organ transplantation/
4. kidney transplantation/
5. pancreas transplantation/
6. exp lung transplantation/
7. exp heart transplantation/
8. liver transplantation/
9. (pancreas$ transplant$ and kidney$ transplant$).tw.
10. simultaneous pancreas kidney transplant$.tw.
11. spk.tw.
12. lung transplant$.tw.
13. heart transplant$.tw.
14. liver transplant$.tw.
15. organ transplant$.tw.
16. kidney transplant$.tw.
17. pancreas transplant$.tw.
18. ((cardiac or hepatic or renal or pancreas-kidney or heart-lung or lung-heart) adj2 (transplant$ or allograft$ or graft$ or donor$ or recipient$)).ti,ab.
19. donat$.ti,ab.
20. or/3-19
21. 1 and 2 and 20
22. exp animals/ not humans/
23. 21 not 22
24. remove duplicates from 23

This search yielded 698 potentially relevant references. Fifty-four references were screened for full text review.

Cohort studies

Narvaez *et al.* Transplant outcomes of donation after circulatory death livers recovered with versus without premortem heparin administration. Liver *Transplantation* 2020;26(2):247-55.

PubMed link: https://pubmed.ncbi.nlm.nih.gov/31755633/

The cohort study compared organ utilisation rates and clinical outcomes of DCD liver transplantation with and without *ante mortem* heparin using US registry data. Of the 5 495 DCD livers recovered for transplant, 589 (10.7 %) did not receive *ante mortem* heparin whilst the remaining 4 906 (89.3 %) received heparin. Liver discard was similar between the no heparin (30.6 %) and heparin groups (30.8 %), respectively (P = 0.90). A multivariate regression analysis adjusted for donor covariates showed that ante mortem heparin status was not a risk factor for discard rate (adjusted OR, 0.97; 95 % CI, 0.80-1.18; P = 0.76). Of 3 754 DCD liver-only transplants, 407 (10.8 %) were from donors who did not receive *ante mortem* heparin and 3 347 (89.2 %) from donors who received *ante mortem* heparin. The cumulative probability of graft survival in the no heparin group was significantly lower compared with the heparin group.

Comparing the no heparin to heparin livers, 1-year graft survival was 73 % and 82 % and 5-year graft survival was 56 % and 65 %, respectively. The adjusted multivariate analysis showed that transplants from DCD livers without *ante mortem* heparin had a higher risk of graft failure and primary non-function compared with those livers that received heparin treatment (adjusted HR, 1.18; 95 % CI, 1.01-1.38; P < 0.05 and 1.81; 95 % CI, 1.17-2.80; P = 0.01, respectively).

Narvaez *et al.* (2019). Outcomes of DCD kidneys recovered for transplantation with versus without pre-mortem heparin administration. *Clin Transplant* 33(7):e13624.

PubMed link: https://pubmed.ncbi.nlm.nih.gov/31162721/

The registry analysis of SRTR (Scientific Registry of Transplant Recipients) data reviewed the organ discard rate and clinical outcomes of DCD kidneys recovered from donors that received heparin versus donors that did not receive heparin. A total of 24 861 DCD kidneys were recovered for transplantation, of which 2 304 did not receive *ante mortem* heparin. The discard rates for no-heparin versus heparin groups were 20.8 % and 19.1 %, respectively (P = 0.05). A multivariate regression adjusted for donor covariates showed that a lack of donor heparin use was not a risk factor for discard (adjusted OR 1.02, 95 % CI 0.89-1.17, P = 0.820). Overall graft survival of the no-heparin group (n = 1791) *versus* the heparin group (n = 17968) was similar on univariate and multivariate analysis (adjusted HR 0.98, 95 % CI 0.87-1.09, P = 0.640). The secondary outcomes mortality, delayed graft function, primary non-function and 1-year eGFR were all similar between groups.

Kamal *et al.* (2015). Outcomes of kidney transplant recipients from donation after circulatory death donors without preagonal heparin administration. Transplantation 99(10):e167-8.

PubMed link: https://pubmed.ncbi.nlm.nih.gov/26426927/

This retrospective, single centre study compared outcomes of 52 kidney transplant recipients who received DCD kidneys that were recovered with (n = 23) or without heparin (n = 29). Heparin administration was decided by the organ procurement organisation. There were no differences between groups for delayed graft function, incidence of acute rejection at 6 months, overall death-censored graft failure, and estimated creatinine clearance at 3, 6 and 12 months. This small study provides limited evidence that early graft function is similar between these groups.

Kramer *et al.* (2020). Donation after circulatory determination of death in western Canada: a multicentre study of donor characteristics and critical care practices. Le don d'organes après décès cardiocirculatoire dans l'Ouest canadien : une étude multicentrique sur les caractéristiques des donneurs et les pratiques de soins intensifs. *Can J Anaesth* 67(5):521-31.

PubMed link: https://pubmed.ncbi.nlm.nih.gov/32100271/

This multicentre, retrospective cohort study from Canada aimed to describe DCD practices in western Canada and report on associations with outcomes. The analysis included 257 potential DCD donors and 321 kidney, 81 liver and 50 lung transplantations were performed. Practices varied across provinces. Heparin was administered in 82 % of potential DCD donors (range across provinces 80–100 %). Heparin was routinely given before or at the time of WLST, or following WLST. When heparin was given to patients that died within two hours of WLST, the median [IQR] number of organs transplanted was 3 [2–4], compared with 3 [2–4] when heparin was not given (P = 0.88). Patient and graft survival rates were not associated with heparin use *versus* withholding of heparin, timing of heparin or heparin dose.

The two studies below do not meet the inclusion criteria but may be of interest:

Butler *et al.* (2014). Normothermic regional perfusion for donation after circulatory death without prior heparinization. *Transplantation* 97 (12): 1272-8.

PubMed link: https://pubmed.ncbi.nlm.nih.gov/24646774/

This single centre report describes the results of a normothermic regional perfusion (NRP) protocol for controlled DCD donors without heparin. Eight DCD donors were treated with NRP. Fourteen kidneys, three livers, two lungs and two pancreases were transplanted. The authors conclude that their protocol has the potential to improve early outcomes of organ retrieved from DCD donors without heparin.

Erasmus *et al.* (2010). Lung transplantation from nonheparinized category III non-heart-beating donors. A single-centre report. *Transplantation* 89(4):452-7.

PubMed link: https://pubmed.ncbi.nlm.nih.gov/20177348/

This small single centre report described their experience using nonheparinised protocol for category III non-heart beating (NHB) donors in adult lung transplantation. Twenty-nine donor procedures resulted in 21 lung transplantations. The NHB outcomes were compared with a group of heart-beating lung transplantations. Primary graft dysfunction, 2-year patient survival, acute rejection episodes and development of bronchiolitis obliterans syndrome was similar between groups. Lung graft function during the first 2 years tended to be better preserved in the NHB group.

Appendix 22. **Single *v.* dual *in situ* cold perfusion in DCD donors**

Summary of findings

None of the studies met the inclusion criteria of the PICO. A few studies were identified for DBD donors and one study in live donor liver transplantation. Overall, the limited data do not consistently show differences between the two perfusion methods.

Clinical question

'Does dual arterial and portal in-situ cold perfusion versus single aortic in-situ cold perfusion in donation after circulatory death (DCD) liver grafts improve transplant rates and/or transplant outcomes?'

PICOS

Population: Adult patients over the age of 18 who proceed to donating the liver following circulatory arrest.

Intervention: Dual arterial and portal *in situ* cold perfusion.

Comparator: Single aortic *in situ* cold perfusion.

Outcomes: The primary outcomes will be the number of organs transplanted from each donor. The secondary outcomes will be early liver function and post-transplant complications.

Study design: Systematic reviews, randomised controlled trials or prospective or retrospective cohort studies.

Search strategy and results

The Transplant Library (TL) was searched from inception to 24 August 2020. The TL includes all randomised controlled trials and systematic reviews in the field of solid organ transplantation published as full text or in abstract form, sourced mainly from MEDLINE/PubMed and hand-searches of congress proceedings.

The search strategy used is as follows:

1. Perfusion/[Limit] Liver Transplantation

Searches identified 86 potentially relevant references. None of the references met the inclusion criteria.

Searches were therefore expanded to include non-randomised studies. We searched MEDLINE and EMBASE from inception to 24 August 2020 using the search strategy below.

1. Perfusion/
2. Organ preservation/mt, st
3. exp Cold ischemia/mt, st
4. exp "Tissue and Organ Procurement"/mt, st
5. (route or single or dual or double or aort$ or arterial or portal or perfusion).ti,ab.
6. or/1-5
7. Hypothermia/
8. Cold temperature/
9. cold.ti,ab.
10. hypothermi$.ti,ab.
11. or/7-10
12. 6 and 11
13. liver transplantation/

14. liver transplant$.ti,ab.
15. hepatectomy/
16. hepatectomy.ti,ab.
17. ((liver or hepatic).ti,ab. or liver/) and (graft$ or transplant$).ti,ab.
18. or/13-17
19. donation after circulatory death.ti,ab.
20. dcd.ti,ab.
21. donation after cardiac death.ti,ab.
22. (non heart-beating or nonheartbeating or non-heart beating or non-heartbeating or nhb$).ti,ab.
23. or/19-22
24. 18 and 23
25. 12 and 24
26. exp animals/ not humans/
27. 25 NOT 26

This search yielded 475 potentially relevant references. None of these studies met the full PICO criteria defined above. However, a small number of studies that may have some relevance to the question are outlined below.

Systematic reviews

No systematic reviews were identified that met the inclusion criteria. However, the following review may be of interest:

Hameed *et al.* (2017). A systematic review and meta-analysis of cold in situ perfusion and preservation of the hepatic allograft: Working toward a unified approach. *Liver Transpl* 23(12):1615-27. DOI:10.1002/lt.24829.

Full text link: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5725662/

The aim of the systematic review was to evaluate the evidence regarding a specific perfusion route (aortic or dual), volume and/or fluid in donation after brain death (DBD) liver transplantation. The extensive literature search was conducted up to February 2017 and the review included 19 unique studies (eight randomised controlled trials (RCTs), one quasi RCT, four prospective cohort studies and six retrospective cohort studies). In the majority of studies (12 out of 19 studies) dual perfusion was used. Meta-analyses were conducted for peak alanine aminotransferase (ALT) and primary non function (PNF). No differences were found between single and dual UW perfusion with respect to PNF (five studies) but peak ALT was significantly lower in the single perfusion group (four studies).

Randomised controlled trials

No RCTs were identified that met the inclusion criteria. However, the following RCT may be of interest:

Shaji *et al.* (2019). Antegrade hepatic artery and portal vein perfusion versus portal vein perfusion alone in living donor liver transplantation: a randomized trial. *Liver Transpl* 25(9):1353-62.

Full text link: https://aasldpubs.onlinelibrary.wiley.com/doi/full/10.1002/lt.25455

This is a good quality RCT in live donor liver transplantation comparing dual or single perfusion. There was a significant difference in the incidence of biliary stricture in the dual perfusion group versus the single perfusion group (6.5 % *versus* 19.4 %, P = 0.04). There was no significant difference in hepatic artery thrombosis (HAT) or biliary leak. The study was not powered to see a difference in HAT, which was a safety concern for the arterial perfusion; however, HAT was actually numerically less in the study group than control group. The 3-graft survival was significantly better in the dual perfusion group compared with the single perfusion group (95.2 % versus 77.4 %, P = 0.004).

Chui *et al.* (1998). Cadaveric liver procurement using aortic perfusion only. *Aust N Z J Surg* 68(4):275-7.

PubMed link: https://pubmed.ncbi.nlm.nih.gov/9572337/

The aim of the randomised controlled trial was to compare aortic perfusion with combined aortic and portal perfusion in donation after brain death (DBD) liver transplantation. The RCT was conducted between 1994 and 1995 and included 40 donors (20 donors in each arm). Peak AST, peak ALT and peak international normalised ratio (INR) were similar.

Cohort studies

No cohort studies were identified that met the inclusion criteria. However, the following cohort study may be of interest:

Hameed *et al.* (2018). Aortic versus dual perfusion for retrieval of the liver after brain death: a national registry analysis. *Liver Transpl*. 24(11):1536-44.

Full text link: https://aasldpubs.onlinelibrary.wiley.com/doi/full/10.1002/lt.25331

The aim of the registry analysis was to report the efficacy of aortic and dual *in situ* perfusion in

donation after brain death (DBD) liver transplantation. Data of adult Australian DBD liver donors and recipients were collected from the Australia and New Zealand Liver Transplant Registry and the Australia and New Zealand Organ Donation Registry between January 2007 and December 2016. (The authors state that 'Donation after circulatory death (DCD) donors could not be included because dual perfusion was not commonly employed in this donor subset'.) A total 1 382 liver transplant recipients were included in the analysis, of which 957 liver were procured using aortic only *in situ* perfusion and 425 liver were procured using dual perfusion. There were no significant differences for the unadjusted 5-year graft survival rates. The overall patient survival rate was significantly lower in the aortic-only group; however, after adjustment for confounders there were no differences between groups. However, a subgroup analysis of higher-risk donors showed that dual perfusion was superior in terms of graft survival.

Appendix 23. **Donation after circulatory death – reporting form (Belgium, English-language version)**

<table>
<tr><td>DCD- Report

Centre : BGETP
Coordinator :
Hospital : …….
…….

ET Donor #:…….

Date: …./…./……..</td><td>Label</td><td colspan="3">DCD Category I ☐ II ☐
III ☐ IV ☐
V (Euthanasia) ☐

Technique:
☐ DBTL catheter Time : … h …
☐ rapid sterno-laparatomy + direct canulation</td></tr>
<tr><td>Start resuscitation procedure
(only for NHBD I and II)</td><td>… h …</td><td colspan="3"></td></tr>
<tr><td>Stop resuscitation procedure
(only for NHBD I and II)</td><td>… h …</td><td colspan="3"></td></tr>
<tr><td>Stop ventilation and supportive therapy</td><td>… h … Extubation: YES /NO Time :
Ré-intubation : YES/NO Time :</td><td rowspan="5">Acirculatory (donor) WIT
= ET
= …… min</td><td rowspan="5">Absolute (donor) WIT
= …… min</td><td rowspan="5">Total (donor) WIT
= ……min</td></tr>
<tr><td>Mean Arterial Pressure < 60 mmHg</td><td>… h …</td></tr>
<tr><td>Asystoly or circulatory arrest
(= start “no touch”)</td><td>… h …</td></tr>
<tr><td>Incision time (= end “no touch”)</td><td>… h …</td></tr>
<tr><td>Start of aortic flush</td><td>… h …</td></tr>
</table>

Time of RIGHT pneumectomy : … h …
Time of hepatectomy : … h …
Time of RIGHT nephrectomy : … h …

Time of LEFT pneumectomy : … h …
Time of pancreatectomy : … h …
Time of LEFT nephrectomy : … h …

Appendix 24. **Donation after circulatory death – reporting form (Netherlands, English-language version)**

ET Donor number: ######

Report generated on: ##.##.2018 ##:##+0100 / Database environment: beta1

Eurotransplant Donor Data

Extra Information Non-Heart-Beating Donor for

General data

Center	Date	Donor Nr	Cadaver type	Contact person	Contact tel.nr.	Contact person OR	Contact tel.nr. OR

ABO	Rh	NHBD category	Reason for Non-heartbeating

Course

Switch off at		Diuresis total (ml)	
Saturation <80% or MAP <50 mmHG at			
Circulatory arrest (mean ABP=0) at			
Cross clamp aorta at			

Explantation/preservation data

DBTL catheter inserted / laparotomy executed at		Carried out by	
Kootstra signs: left		Catheter insertion checked with röntgen	
right		Perfusion technique	

Clinical data

Date	Sys. bloodpressure mm HG	Dia. bloodpressure mm HG	Heart freq. /min	Saturation %	Diuresis ml	Breath freq. /min	Comments

Appendix 25. **Biovigilance standardised notification form for adverse events and reactions (France, English-language version)**

BIOVIGILANCE NOTIFICATION FORM

(Source : Agence de la biomédecine - FRANCE)

ORGAN ☐
TISSUE ☐
CELLS ☐
Ancillary therapeutic products ☐

Cadre réservé à l'ANSM
Fiche BV N°

1. Reporter

To be filled up by the reporter	***To be filled up by the local biovigilance coordinator (LBC)***
Identity of the reporter Surname: First name:	Identity of the LBC Surname: First name:
Title:	Title:
Details of the reporter Telephone number: Fax : E-mail : Address :	Details of the local biovigilance coordinator Telephone number: Fax : E-mail : Address :
	Date of notification λ_____μ λ_____μ λ_____μ
	Internal reference number:
	☐ initial notification ☐ notification follow-up (specify the BV number)

2. Product(s) concerned

Type of graft, identification number ☐ Allogeneic ☐ Autologous	
Name of the ATP (1), producer, batch number	
Location of the preparation* or location of the procurement * or producer's address* (regarding ATP)	
Specify, if need be, if : ☐ the graft or product was imported ☐ the graft or product was exported Origin*/destination* of the import*/export* : Date of import*/export* : λ_____μ λ_____μ λ_____μ	

(1) ATP: Ancillary Therapeutic Product (preservation liquid, media)* Delete whichever does not apply

3. Donor and recipient(s) involved *(or potentially involved)*

Donor			
Status : ☐ Living ☐ BD & HB (2) ☐ DCD (3) ☐ PMT (4) Donation between relatives : ☐ yes ☐ no			
Identification N°:	Sex : ☐ M ☐ F	Birth date: λ_____μ λ_____μ λ_____μ	
Date of procurement: λ_____μ λ_____μ λ_____μ	Location of the procurement:		
Recipient			
Identification N°:	Sex : ☐ M ☐ F	Birth date: λ_____μ λ_____μ λ_____μ	
Date of transplantation: λ_____μ λ_____μ λ_____μ	Location of the transplantation:		

Other organ and/or tissue** and/or cells** **recipients**: ☐ yes (specify in the table below) ☐ no

Identification N°					
Type of graft					
Date of transplantation	λ___ λ___ λ_____	λ___ λ___ λ_____	λ___ λ___ λ_____	λ___ λ___ λ_____	λ___ λ___ λ_____
Location of the transplantation (hospital and city)					

**: With regard to tissues and cells, specify the name of the tissue bank or the cell therapy unit concerned

(2) BDD&HBD: brain-death donor and heart-beating donor; (3) DCD: donor after circulatory-death leading to the implementation of organ preservation techniques. (4) PMT: post-mortem tissues retrieved at the morgue

4. Description of the adverse event and/or reaction

If need be, attach a more exhaustive description on a plain unheaded paper. Specify the number of attached pages (Please write the name of the sender on each page):

Date (of occurrence*or detection*)

λ_____μ λ_____μ λ_____μ

☐ of the event

☐ of the adverse reaction (donor* or recipient*)

* Delete whichever does not apply

Description:

Level of the adverse reaction:

Initial ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5

Final ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5

1-Insignificant: clinical or biological manifestations that do not need any care or medical treatment.

2-Moderate: clinical or biological manifestations presenting with no vital threat on the short or long term. Hospitalisation is not necessary.

3-Severe: clinical or biological manifestations :

- leading to disability or incapacity,
- inducing, prolonging or complicating hospitalisation or any other morbid state or,
- necessitating medical or surgical intervention to preclude permanent damage or impairment of a body function.

Important: Serious infections likely to be transmitted by the graft or during procurement or transplantation must be systematically declared at a severity level higher than or equal to 3.

4-Major: imminent vital threat

5-Death

Investigation: ☐ pending ☐ not performed* ☐ not performable*

☐ completed – closing date : λ_____μ λ_____μ λ_____μ

Detail the analysis of the causes (and their conclusion when investigation has been completed)

* If the investigation has not been performed, please explain the reasons for taking this decision

Imputability (link between the product or the procurement or the transplantation activity and the adverse reaction at the beginning and at the end of the investigation):

Initial: ☐ 1-Excluded/unlikely ☐ 2- Possible ☐ 3- Likely/probable ☐ 4- Certain ☐ not assessable

Final: ☐ 1-Excluded/unlikely ☐ 2- Possible ☐ 3- Likely/probable ☐ 4- Certain ☐ not assessable

5. Local assessment of the criticality and of the measures taken

Probability of recurrence of the adverse event or reaction (probability that the event occurs again in view of the controls implemented) :

☐ R1-rare ☐ R2-unlikely ☐ R3-possible ☐ R4-likely ☐ R5-almost certain ☐ not assessable

Potential consequences of the adverse reaction or event on the patients, on the stock of grafts or on ATP

☐ C1 ☐ C2 ☐ C3 ☐ C4 ☐ C5 ☐ not evaluable

1-**Insignificant** (no clinical and/or biological manifestations or no consequence for the stock of products).

2-**Moderate** (moderate clinical and/or biological manifestations that do not absolutely require medical intervention or treatment or to report transplantation or applications).

3-**Serious** (disability or permanent incapacity, medical intervention and treatment or cancellation or delay in several transplantations or applications).

4-**Major** (vital threat for the patient(s) or significant number of transplantations or applications cancelled that request the use of imported products).

5-**Extreme** (death of the patient(s) or cancellation of all transplantations and applications).

Description of the measures locally implemented to reduce criticality (RxC)

6. Dissemination of information

Other biovigilance correspondent(s) informed: ☐ No ☐ Yes (specify location and date)

The biomedicine Agency (SRA* and/or biomedicine Agency's LBC) was informed on: λ_____μ λ_____μ λ_____μ

Other vigilance body(ies) informed: ☐ No ☐ Yes (specify)

Other transplantation team(s) informed : ☐ No ☐ Yes (specify location and date)

Date and reporter's signature

Date and signature of the local biovigilance correspondent

*Regional unit

Appendix 26. **Incident notification form, Germany (English-language version)**

INITIAL REPORT Organs

about serious adverse events (SAE) or
serious adverse reactions (SAR)
according to § 10 section 1 TPG-OrganV

Reporting member state: Germany
Report number: DEU/276

DEUTSCHE STIFTUNG ORGANTRANSPLANTATION
Gemeinnützige Stiftung
Koordinierungsstelle Organspende

ET Donor-No.: **Date of procurement:** **Donor region / country:**
DSO Donor-No.: **Donor age:** years

Description of SAE/SAR

Date/time of occurrence of SAE/SAR: **at**
Date/time of detection of SAE/SAR: **at**
SAE/SAR incident submitted: **at** **by**
Date/time of this initial report: **at**

Organs transplanted from this donor

Organ	Recipient centre	ET Recipient-No.
Heart		
Lung left		
Lung right		
Kidney left		
Kidney right		
Liver		
Liver split left		
Liver split right		
Pancreas		
Intestine		

Supplementary details

In case of questions please contact the SAE/SAR team of the DSO (24/7):

Telephone national 0800 376 7273
Telephone international +49 69 677 328 9998
Fax +49 69 677 328 89998
E-Mail dso.sare@dso.de

Deutschherrnufer 52
60594 Frankfurt/Main - Germany
www.dso.de

INITIAL REPORT SAE/SAR Organs ET Spender-Nr.

Immediate action taken / urgent measures suggested

Please fill in the attached doctor's report regarding the current health status of your recipient and send it by fax or email to the below mentioned contact data within 3 working days.

This document has been generated electronically – no signature required.

In case of questions please contact the SAE/SAR team of the DSO (24/7):

Telephone national 0800 376 7273
Telephone international +49 69 677 328 9998
Fax +49 69 677 328 89998
E-Mail dso.sare@dso.de

Deutschherrnufer 52
60594 Frankfurt/Main - Germany
www.dso.de

INTERIM REPORT Organs

about serious adverse events (SAE) or
serious adverse reactions (SAR)
according to § 10 section 1 TPG-OrganV

Reporting member state: Germany
Report number: DEU/276

DEUTSCHE STIFTUNG ORGANTRANSPLANTATION
Gemeinnützige Stiftung
Koordinierungsstelle Organspende

ET Donor-No.: **Date of procurement:** **Donor region / country:**
DSO Donor-No.: **Donor age:**

Description of SAE/SAR

Date/time of occurrence of SAE/SAR: **at**
Date/time of detection of SAE/SAR: **at**
Date of the initial report:
Date/time of this interim report: **at**

Organs transplanted from this donor

Organ	Recipient centre	ET Recipient-No.
Heart		
Lung left		
Lung right		
Kidney left		
Kidney right		
Liver		
Liver split left		
Liver split right		
Pancreas		
Intestine		

Supplementary details

This document has been generated electronically – no signature required.

In case of questions please contact the SAE/SAR team of the DSO (24/7):

Telephone national 0800 376 7273
Telephone international +49 69 677 328 9998
Fax +49 69 677 328 89998
E-Mail dso.sare@dso.de

Deutschherrnufer 52
60594 Frankfurt/Main - Germany
www.dso.de

INTERIM REPORT SAE/SAR Organs ET Spender-Nr.

In case of questions please contact the SAE/SAR team of the DSO (24/7):

Telephone national 0800 376 7273
Telephone international +49 69 677 328 9998
Fax +49 69 677 328 89998
E-Mail dso.sare@dso.de

Deutschherrnufer 52
60594 Frankfurt/Main - Germany
www.dso.de

FINAL REPORT Organs

about serious adverse events (SAE) or
serious adverse reactions (SAR)
according to § 10 section 2 TPG-OrganV

Reporting member state: Germany
Report number: DEU/276

DEUTSCHE STIFTUNG ORGANTRANSPLANTATION
Gemeinnützige Stiftung
Koordinierungsstelle Organspende

ET Donor-No.: **Date of procurement:** **Donor region / country:**
DSO Donor-No .: **Donor age:**

Description of SAE/SAR

Final diagnosis of SAE/SAR

Date of the initial report:
Date of the interim report:
Date/time of this final report: **at**

Organs transplanted from this donor

Organ	Recipient centre	ET Recipient-No.
Heart		
Lung left		
Lung right		
Kidney left		
Kidney right		
Liver		
Liver split left		
Liver split right		
Pancreas		
Intestine		

Result of examinations and conclusion

Preventive and corrective measures

In case of questions please contact the SAE/SAR team of the DSO (24/7):

Telephone national 0800 376 7273
Telephone international +49 69 677 328 9998
Fax +49 69 677 328 89998
E-Mail dso.sare@dso.de

Deutschherrnufer 52
60594 Frankfurt/Main - Germany
www.dso.de

FINAL REPORT SAE/SAR Organs ET Spender-Nr.

Implications and possible follow-up actions

In case of questions please contact the SAE/SAR team of the DSO (24/7):

Telephone national 0800 376 7273
Telephone international +49 69 677 328 9998
Fax +49 69 677 328 89998
E-Mail dso.sare@dso.de

Deutschherrnufer 52
60594 Frankfurt/Main - Germany
www.dso.de

DOCTOR'S REPORT

SAE/SAR – transplanted recipient

DEUTSCHE STIFTUNG ORGANTRANSPLANTATION
Gemeinnützige Stiftung
Koordinierungsstelle Organspende

Name of reporting physician: _____
ET Donor-No.: _____
ET Recipient Centre-Code: _____
ET Recipient-Number: _____

Current health status of recipient with reference to the reported SAE/SAR
(Please attach original reports)

_____

_____

_____

_____

_____

_____

_____

_____

_____

_____

_____

_____

_____
Signature

Please return to the below mentioned contact data within 3 working days.

In case of questions please contact the SAE/SAR team of the DSO (24/7):

Telephone national 0800 376 7273
Telephone international +49 69 677 328 9998
Fax +49 69 677 328 89998
E-Mail dso.sare@dso.de

Deutschherrnufer 52
60594 Frankfurt/Main - Germany
www.dso.de

Appendix 27. **Incident notification form, United Kingdom**

INCIDENT SUBMISSION FORM

NHS Blood and Transplant

Is incident deemed urgent and requires immediate action? ○ No ○ Yes, not notified by phone ○ Yes, already notified by phone

You will be unable to complete the rest of this form until you answer the question above.

- Fields marked with * are mandatory, all other fields can be completed, if relevant, to provide information about the incident. For help completing fields, click on
- To avoid losing data, please be aware this form will time out after **30 minutes** of inactivity and must be completed and submitted at the same time; it is not possible to partially complete the form and return to it later.
- In order to complete the form, please ensure that you have the relevant details and patient reference numbers to hand.

Submitter Details

First name | Job title

Last name | Email address

Phone number | Re-enter Email address

Incident Details

Date and time incident identified *

dd-mm-yyyy hh:mm

Details of incident and further action taken. In reports whereby photographs would provide further information, such as organ assessment or damage, please attach to enable a more beneficial review *

Max. 2000 characters

Attachments
Attachments are limited to a maximum of 10mb in size each. A maximum of 5 attachments may be added

Choose file No file chosen

Donor ID status *
- ID not allocated
- Not related to an individual donor
- Donor ID

NHSBT donor ID number(s) and type(s) involved in this incident

Please Select

Recipient ID status *
- ID not allocated / not known
- Not related to an individual recipient
- Recipient ID

ID number(s) of the recipient involved in this incident?

Details Of Those Involved Relevant To The Report

04/06/2021 NHSBT Incident Submission Form

Organ Donation Services Team (ODST)
Please Select

Transplant Centre
Please Select

Retrieval Team
Please Select

Coroner / Procurator Fiscal jurisdiction
Enter Coroner / Procurator Fiscal jurisdiction name

Donating hospital – search by town / city
Please type town and select from list, if not listed enter name and town

Microbiology / Virology lab
Please type town and select from list, if not listed enter name and town

NHSBT site where incident occurred
Please Select

Haematology / Biochemistry lab
Please type town and select from list, if not listed enter name and town

H & I lab
Please Select

Histo-pathology lab
Please type town and select from list, if not listed enter name and town

Additional Information

The incident has also been reported to these organisations
Select organisation(s)
Please Select

Reference numbers for reports to other organisations
One per line. Please list organisation reference number

- To print a copy of this form and the incident details please use the browser's print function BEFORE submitting the form
- Form data can be saved in pdf format AFTER the incident has been submitted
- As this form only recently went live we are interested in your feedback about how you found completing this form. Please send any feedback to NHSBT at clinicalgovernance.odt@nhsbt.nhs.uk

Submit

Appendix 28. **Informed-consent checklist for transplant recipients (United Kingdom)**

Benefits, risks and implications associated with solid organ transplantation (NHS Blood and Transplant and British Transplantation Society)

1. General risks	
	a. Transmission of donor cancer
	I. known current/past medical history
	II. unknown
	b. Transmission of donor infection
	I. identified (CMV, EBV, HBV, HCV, HTLV, HIV, syphilis)
	II. unknown

2. Transplant related risks	
	a. Increased cardiovascular morbidity and mortality
	b. Immunosuppression
	I. general side-effects • increased risk of some *de novo* cancers, especially skin and lymphoma • increased risk of some infections • increased weight • increased risk of diabetes mellitus
	II. drug-specific side-effects • corticosteroids • calcineurin-inhibitors • anti-proliferatives (mycophenolate, azathioprine) • mTOR inhibitors • others

3. Organ-specific risks	
	a. Risk of death on the waiting list
	b. Patient and graft survival probability
	c. Risks of specific organ complications
	d. Risks associated with types of
	I. donor (such as DCD and DBD)
	II. graft (such as split or damaged organ)
	e. Re-graft and access to re-graft
	f. Risk of non-function
	g. Risk of delayed function
	h. Need for renal support
	i. Recurrent disease

4. Lifestyle issues	
	a. Need for compliance with
	I. immunosuppression II. outpatient attendances and monitoring
	b. Lifestyle
	I. alcohol and illicit drug use II. pregnancy and sexual health III. travel and immunisations

5. Benefits	
	a. Improved survival
	b. Improved quality of life

Appendix 29. **Informed-consent checklist for transplant recipients at the time of the organ offer**

Benefits, risks and implications associated with solid organ transplantation

(adapted from NHS Blood and Transplant and British Transplantation Society* and White *et al.* 2019†)

1. Donor information	
	a. Age range (by decade)
	b. Gender
	c. Type of death (such as trauma or cerebrovascular event)
	d. Type of donor (DCD or DBD)

2. Donor related risks	
	a. Whether the donor poses a greater risk of transmission of infection or malignancy
	(This applies when the transplant candidate has expressed willingness to accept these donor organ types previously) I. the infection(s) that may be transmitted and the likely risk of transmission II. the potential severity of infection III. the ease of treating the infection should transmission occur IV. whether all testing of the donor has been completed V. the risk of significant morbidity or mortality without transplantation at this time VI. benefit of accepting this organ at this time The same applies in the event of a greater risk of transmission of malignancy
	b. Whether the donor organ has a particular risk of poor function and other factors potentially affecting short- and long-term graft function
	I. age of donor II. cause of death of donor III. type of donor: DCD compared with DBD, the nature of the risk varying between organs IV. higher body mass index of donor V. length of stay in an ICU prior to donation VI. split or reduced liver VII. longer warm and cold ischaemia times

* NHSBT/BTS. Policy POL191/2: *Guidelines for consent for solid organ transplantation in adults*, 2015, available at https://nhsbtdbe.blob.core.windows.net/umbraco-assets-corp/4378/guidelines_consent_for_solid_organ_transplantation_adults.pdf.

† White SL, Rawlinson W, Boan P *et al.* Infectious disease transmission in solid organ transplantation: donor evaluation, recipient risk, and outcomes of transmission. *Transplant Direct* 2019;5(1):e416.

3. Donor information NOT to be transmitted to recipients	
	I. name (or initials) II. occupation or social class III. date of birth IV. place of donation V. ethnicity

4. Donor information to be transmitted to recipients upon request	
	VI. sexual, alcohol or drug history

Appendix 30. **Living donor informed consent checklist (UNOS)**

This checklist contains elements typically reviewed as part of OPTN routine survey activities of living donor recovery hospitals. Use of this checklist is not an OPTN obligation and does not guarantee an assessment of compliance with OPTN obligations upon a site survey. This checklist is intended to guide the development of centre-specific processes and tools.

The living donor recovery hospital is responsible for obtaining and documenting informed consent prior to organ recovery. Informed consent requirements apply to living kidney, liver, pancreas, intestine, and lung donors and must include all of the components listed below. Documentation of informed consent must be maintained in the living donor medical record.

All living donors

Obtain from living donors	
	The living donor's signature on a document that confirms that the donor: • is willing to donate • is free from inducement and coercion • has been informed that he or she may decline to donate at any time

Provide to living donors	
	1. An opportunity to discontinue the living donor consent or evaluation process in a way that is protected and confidential.
	2. The ILDA must be available to assist the living donor during the consent process, according to *Policy 14.2: Independent Living Donor Advocate (ILDA) Requirements*.
	3. Instruction about all phases of the living donation process, which includes: • consent • medical and psychosocial evaluations • pre- and post-operative care • required post-operative follow-up according to *Policy 18.5: Living Donor Data Submission Requirements*. (Teaching or instructional material can include any media, one-on-one or small group interaction. Teaching or instruction must be provided in a language in which the living donor is able to engage in meaningful dialogue with recovery hospital's staff.)

Disclose to living donors	
	1. It is a federal crime for any person to knowingly acquire, obtain or otherwise transfer any human organ for anything of value including, but not limited, to cash, property, and vacations.
	2. The recovery hospital must provide an ILDA.
	3. Alternate procedures or courses of treatment for the recipient, including deceased donor transplantation.
	4. A deceased donor organ may become available for the candidate before the recovery hospital completes the living donor's evaluation or the living donor transplant occurs.
	5. Transplant hospitals determine candidacy for transplantation based on existing hospital specific guidelines or practices and clinical judgment.
	6. The recovery hospital will take all reasonable precautions to provide confidentiality for the living donor and recipient.
	7. Any transplant candidate may have an increased likelihood of adverse outcomes (including but not limited to graft failure, complications, and mortality) that: • exceed local or national averages • do not necessarily prohibit transplantation • are not disclosed to the living donor
	8. The recovery hospital can disclose to the living donor certain information about candidates only with permission of the candidate, including: • the reasons for a transplant candidate's increased likelihood of adverse outcomes • personal health information collected during the transplant candidate's evaluation, which is confidential and protected under privacy law
	9. Health information obtained during the living donor evaluation is subject to the same regulations as all medical records and could reveal conditions that must be reported to local, state, or federal public health authorities.
	10. The recovery hospital is required to: • report living donor follow-up information, at the time intervals specified in *Policy 18.5: Living Donor Data Submission Requirements* • have the donor commit to post donation follow-up testing co-ordinated by the recovery hospital.
	11. Any infectious disease or malignancy that is pertinent to acute recipient care discovered during the donor's first two years of follow-up care: • May need to be reported to local, state or federal public health authorities • Will be disclosed to their recipient's transplant hospital • Will be reported through the OPTN Improving Patient Safety Portal
	12. A living donor must undergo a medical evaluation according to *Policy 14.4: Medical Evaluation Requirements for Living Donors* and a psychosocial evaluation as required by *Policy 14.1: Psychosocial Evaluation Requirements for Living Donors*.
	13. The hospital may refuse the living donor. In such cases, the recovery hospital must inform the living donor that a different recovery hospital may evaluate the living donor using different selection criteria
	14. The following are inherent risks associated with evaluation for living donation: • allergic reactions to contrast • discovery of reportable infections • discovery of serious medical conditions • discovery of adverse genetic findings unknown to the living donor • discovery of certain abnormalities that will require more testing at the living donor's expense or create the need for unexpected decisions on the part of the transplant team

15. There are surgical, medical, psychosocial, and financial risks associated with living donation, which may be temporary or permanent and include, but are not limited to, *all* of the following:

a. Potential medical or surgical risks:
- death
- scars, hernia, wound infection, blood clots, pneumonia, nerve injury, pain, fatigue, and other consequences typical of any surgical procedure
- abdominal symptoms such as bloating, nausea, and developing bowel obstruction
- that the morbidity and mortality of the living donor may be impacted by age, obesity, hypertension, or other donor-specific pre-existing conditions

b. Potential psychosocial risks:
- problems with body image
- post-surgery depression or anxiety
- feelings of emotional distress or grief if the transplant recipient experiences any recurrent disease or if the transplant recipient dies
- changes to the living donor's lifestyle from donation

c. Potential financial impacts:
- personal expenses of travel, housing, child care costs, and lost wages related to donation might not be reimbursed; however, resources might be available to defray some donation-related costs
- need for life-long follow up at the living donor's expense
- loss of employment or income
- negative impact on the ability to obtain future employment
- negative impact on the ability to obtain, maintain, or afford health insurance, disability insurance, and life insurance
- future health problems experienced by living donors following donation may not be covered by the recipient's insurance

Living kidney donors – additional requirements

Provide to all living kidney donors

Education about expected post-donation kidney function, and how chronic kidney disease (CKD) and end-stage renal disease (ESRD) might potentially impact the living donor in the future, to include:
a. On average, living donors will have a 25-35 % permanent loss of kidney function after donation.
b. Although risk of ESRD for living kidney donors does not exceed that of the general population with the same demographic profile, risk of ESRD for living kidney donors may exceed that of healthy non-donors with medical characteristics similar to living kidney donors.
c. Living donor risks must be interpreted in light of the known epidemiology of both CKD and ESRD. When CKD or ESRD occurs, CKD generally develops in mid-life (40-50 years old) and ESRD generally develops after age 60. The medical evaluation of a young living donor cannot predict lifetime risk of CKD or ESRD.
d. Living donors may be at a higher risk for CKD if they sustain damage to the remaining kidney. The development of CKD and subsequent progression to ESRD may be faster with only one kidney.
e. Dialysis is required if the living donor develops ESRD.

Current practice is to prioritize prior living kidney donors who become kidney transplant candidates according to *Policy 8.3: Kidney Allocation Points*.

Disclose to all living kidney donors

Surgical risks may be transient or permanent and include but are not limited to:
- decreased kidney function
- acute kidney failure and the need for dialysis or kidney transplant for the living donor in the immediate post-operative period

Disclose to all female living kidney donors

Risks of preeclampsia or gestational hypertension are increased in pregnancies after donation

Living liver donors – additional requirements

Disclose to all living liver donors

Surgical risks may be transient or permanent and include but are not limited to:
- acute liver failure with need for liver transplant.
- transient liver dysfunction with recovery. The potential for transient liver dysfunction depends upon the amount of the total liver removed for donation.
- risk of red cell transfusions or other blood products.
- biliary complications, including leak or stricture that may require additional intervention.
- post-donation laboratory tests may result in abnormal or false positive results that may trigger additional tests that have associated risks.

As part of the informed consent process, recovery hospitals must also provide transplant recipient outcome and transplanted organ survival data to all living donors.

Outcomes data

If the recovery hospital and the recipient hospital are the same	
	Then the recovery hospital must provide the living donor with both national and that hospital's program-specific transplant recipient outcomes from the most recent Scientific Registry of Transplant Recipients (SRTR) program-specific reports, including all the following information: 1. National 1-year patient and transplanted organ survival 2. The hospital's 1-year patient and transplanted organ survival 3. Notification about all Centers for Medicare and Medicaid Services (CMS) outcome requirements not being met by the transplant hospital

If the recovery hospital and the recipient hospital will not be the same and the recipient hospital is known	
	Then the recovery hospital must provide the living donor with both national and the recipient hospital's program-specific transplant recipient outcomes from the most recent SRTR program-specific reports, including all the following information: 1. National 1-year patient and transplanted organ survival 2. The recipient hospital's 1-year patient and transplanted organ survival 3. Notification about all CMS outcome requirements not being met by the recipient hospital

If the recovery hospital and the recipient hospital will not be the same and the recipient hospital is not known	
	Then the recovery hospital must provide the living donor with national transplant recipient outcomes from the most recent SRTR reports, including national 1-year patient and transplanted organ survival.

Appendix 31. Plain language version of Living Donor informed-consent requirements (Organ Procurement and Transplantation Network – OPTN)

Thinking about being a living donor? This is what you need to know first.

This paper explains what you need to know before you may agree to be a living organ donor. It is a patient version of the OPTN (Organ Procurement and Transplantation Network) informed consent policy. This paper explains:

- what it means to give your consent
- that only you can decide to donate
- you have the right to privacy as you get tested and make your decision
- the role of an Independent Living Donor Advocate
- what the transplant hospital staff must do before, during and after donation
- the risks of living organ donation, including the medical, mental, social and financial risks
- how your health might be affected by donation
- what information you must be given about how well transplant recipients do after their transplants
- what information about your organ recipient you do not have the right to receive
- your need for medical follow-up after donation.

A living donor can donate a:

- kidney
- portion of their liver, pancreas or intestine
- lobe of their lung

Some words used in this paper and their meaning may be helpful.

- A person who needs an organ transplant is called a 'transplant candidate'. A transplant candidate must be on the national waiting list to receive an organ transplant from a deceased donor or a living donor.
- After a transplant candidate receives an organ transplant they are called a 'transplant recipient' or 'recipient'.
- If the living donor knows the recipient it is 'directed donation'.
- If the living donor does not know the recipient it is 'non-directed donation'.

You will meet with the hospital staff who will help you decide if you can be a living donor. The hospital staff must get your informed consent. Through informed consent, the hospital staff gives you information so that you understand the benefits and risks of donor testing and organ donation, and that you agree to the testing and donation. Informed consent will include all the items below.

1 Consent for Living Donation

To become a living donor you must be able to state that:

- you want to donate
- no one forced you to donate

- no one said they would give you something of value for donating
- you know that you can decide not to donate at any time.

The hospital staff will ask you to sign a paper for your medical record to show you understand these things.

2 Living Donation is Your Choice

You Have a Right to Privacy as You Get Tested and Make Your Choice

It is your choice to donate an organ. It is against the law for you to receive something like cash, property or a vacation for donating an organ.

If you become a living donor, the hospital staff must keep your personal and medical information private. The hospital staff must also keep the recipient's personal information private.

If you want to be a non-directed donor, the hospital staff must keep your identity private. The hospital staff must also keep the identity of the recipient private.

If you decide not to donate, the hospital staff will keep your decision and reasons private.

3 The Independent Living Donor Advocate (ILDA)

The hospital staff will provide an independent living donor advocate (ILDA). An ILDA is a person who understands the organ donation process and who will

1. promote your best interests.
2. check that you have received information about the following topics:

   - the informed consent process
   - the tests needed to be a living donor, and the risks of these tests
   - the surgery, and the care you will get after the surgery
   - the need to have follow-up care after donation

3. help you get more information about these topics as needed. The ILDA should not be involved with the transplant candidate.

4 Hospital Staff Responsibilities

The hospital staff will tell you about the donation process. The staff must give you information using words that you understand so that you can ask questions.

To be a living donor, you must have medical tests to make sure you are healthy enough to donate an organ. The hospital staff will help you understand the medical tests that will be needed. The hospital staff will also make sure you are ready mentally to be a donor and have a plan for your recovery (for example, whether you can take time off from work and who will help you while you recover). This is called a psychosocial evaluation. Your ILDA will make sure you understand the steps in these evaluations. Your ILDA will get answers to any questions you have about testing, the use of personal information and any other questions you have about donating.

After the tests, the hospital staff may decide that you should not be a living donor. If this happens, the hospital staff should tell you that you could be evaluated at a different hospital. Another hospital might decide that you may donate because every hospital uses its own guidelines and judgment.

During the tests, the hospital staff may find that you have a medical condition that you did not know about. You could need to be treated for this condition. Also, the hospital staff could find that you have an infection or sexually-transmitted disease that you did not know about. It is the law that hospitals must report some of those conditions to local, state or federal public health authorities. They must report them privately, meaning that no one else will be told.

The hospital staff must tell you that transplant candidates have other options for treatment. A transplant candidate could get an organ from a deceased donor instead of from you. A transplant candidate who needs a kidney transplant could continue to get dialysis if they do not receive a transplant.

After you donate an organ, your hospital must continue to check on your health. Depending on the type of organ you donate, the hospital must report information about your health and personal status (e.g. ability to work) for two years after you donate. You must agree to take part in this follow-up. Ask the hospital staff how you will receive follow-up and who will pay for the follow-up.

A group called the Scientific Registry of Transplant Recipients (SRTR) collects and keeps information for every transplant hospital in this country. The information shows how well recipients do on average after getting transplants. The hospital staff must give you information about how well recipients do at the hospital performing the recipient's transplant, if the transplant hospital is known in advance. The information must include

- percentage of transplant recipients at that hospital still alive one year after transplant

- percentage of transplanted organs at that hospital still functioning one year after transplant
- percentage of transplant recipients alive and transplanted organs functioning after one year, in the country overall.

If the transplant centre is not known, staff at your donation hospital must give you information about

- the percentage of transplant recipients across the country who are alive after one year
- the percentage of transplanted organs functioning after one year across the country.

Ask your ILDA if you need help understanding this information.

5 Information You Do Not Have a Right to Receive

The hospital staff can only give you some information about the transplant candidate if the candidate agrees. This information includes

- any reasons why the transplant candidate may have increased risk for a bad result after getting the transplant
- any personal health information about the candidate that the law says is private.

The transplant candidate could have a bad result after the transplant. A bad result could be, for example, that the organ transplant does not work, the recipient has new medical problems or the recipient dies. The chance of one of these things happening to the recipient of your organ might be higher than it would be for other transplant candidates. The hospital might decide that the recipient would still benefit and that the transplant should happen anyway. The hospital staff is not allowed to tell you about the transplant candidate's chances of having a bad outcome unless the transplant candidate agrees to share the information. Each hospital chooses potential donors and transplant candidates based on the hospital's own guidelines, practices and judgment.

6 Risks of Donation

The hospital staff must make sure you know about the following risks. Ask your ILDA to explain any risks you do not understand.

Potential medical risks that could happen during the evaluation:

- Being allergic to a test and having a bad reaction.
- Discovery of an infection the hospital staff need to report.
- Discovery of a serious medical condition that could require more medical tests or treatment that you will have to pay for.
- Discovery of a genetic health risk factor or issue that you did not know about.

Potential surgical or medical risks that could happen if you donate an organ:

- Death or disease (being very overweight, older or having high blood pressure or other medical conditions could make you more likely to die or have a problem).
- Scars, hernia, infection, blood clots, pneumonia, nerve injury, pain, tiredness and other symptoms that are common when people have surgery.
- Abdominal symptoms like bloating, nausea or having a bowel obstruction.

Potential mental or social risks after donating:

- Problems with how you feel about your body or what it looks like.
- Problems with depression or fear and stress.
- Feeling sad if the transplant recipient becomes ill or dies.
- Changes in your lifestyle because you donated an organ.

Potential money problems after donating:

- Paying for travel, short-term housing and child care, and not being paid while you were away or recovering from surgery. Some money may be available to help you with such non-medical donation-related costs.
- Having to pay for costs of lifelong follow-up visits.
- Losing your job or your income.
- Having a hard time finding a job in the future.
- Having a hard time getting, keeping or paying for health insurance, disability insurance and life insurance.
- Future health problems that may not be covered by the transplant recipient's insurance.

7 Effect on Your Future Health

Living Kidney Donors

If you donate a kidney, hospital staff must tell you about how living kidney donation relates to ongoing or chronic kidney disease and kidney failure. Your ILDA should help you understand these terms.

If you are thinking about donating a kidney, you should know these facts:

- On average, you will permanently lose 25-35 % of your kidney function after donating.
- Your risk of having kidney failure later in your life is not any higher than it is for someone in the general population of a similar age, sex or race. However, you are more likely to have kidney failure than healthy people who are not donors.
- Chronic kidney disease most often starts in the middle of your life (40-50 years old). Kidney failure most often starts after age 60. If you get tested when you are young, doctors cannot predict how likely you are to have chronic kidney disease or kidney failure later in life.
- If you damage your other kidney (the one you did not donate), you may have a higher chance of having chronic kidney disease, which could go on to become kidney failure.
- You will need medical treatment if you start to have kidney failure.
- Current policy gives living donors priority on the national waiting list if they need to get a kidney transplant in the future. You can ask your ILDA or another transplant hospital staff member about this policy.

These events and others could happen during or after surgery, and they could be short-term or permanent:

- You will lose some of your kidney function.
- You could have kidney failure and need dialysis.
- If you become pregnant after donating, you are more likely to have high blood pressure during pregnancy. This is called 'pre-eclampsia'.

Living Liver Donors

If you are thinking about donating part of your liver, you should know that these events and others could happen during or after surgery, and they could be short-term or permanent:

- You could have immediate liver failure and need a transplant.
- You could have temporary liver problems while you recover. This may depend on how much of your liver you donate.
- You may need a blood transfusion.
- Your liver may leak and you may need another operation to fix the leak.
- You may need more tests after you donate, which might also have risks.

8 After You Become a Living Donor

You must agree to give information about your health and general status to the hospital where you donated for two years after donation. The reason you need to have this medical follow-up is to check your health and to give you medical treatment as needed.

During this follow-up, like during any medical checkup, tests might show that you have a medical problem that could need to be treated, and the cost of the treatment might not be covered by the recipient's insurance. Also, if an infectious or sexually-transmitted disease is found, the hospital staff may need to report it, in confidence, to local, state or federal public health authorities, the transplant recipient's hospital and to the OPTN. The hospital staff will not share this information with your recipient, your family or any other person the staff is not required to tell by law.

If you have any questions or concerns about any step of living donor evaluation, donation or follow-up, ask your transplant hospital team.

Appendix 32. **Recommendations for communicating risks to potential living organ donors**

1. Start early	It may take weeks or months before donors have learned enough about the short- and long-term risks to be able to make an informed decision about donation.
2. Use written materials to inform and explain	Written materials describing risks, using numbers and examples, help donors to understand. Such materials can be used both as teaching tools and as a basis for later discussions. Materials should be developed and tested in different demographic groups, and should be at an appropriate reading level.
3. Allow time	Some (but not all) donors need weeks or months to learn about the potential risks and to consider different aspects of donation. Let them have time to gather and process information.
4. Information should precede examinations	Education and information about risks should be well ahead of different physical examinations to ensure that potential donors are well informed on donation- and evaluation-related risks when they undergo the evaluation.
5. Consider using standardised questionnaires	Standardised forms for donors to answer may serve as a quality control to ascertain that the donor has received adequate information about donation-related risks, or to find out where there is potential for increasing the donor's knowledge.
6. Teaching back	Encourage the potential donor to "teach back" by telling the transplant professional about the risks associated with donation. This may serve simultaneously to assess the donor's comprehension and to distinguish between the donor's perception of risks and the objective risks.
7. Try to express risks neutrally as numbers	Health personnel are allowed to use qualitative expressions such as "high" or "low" regarding donation-related risks, but it may be even more important to express risks as numbers or percentages. For example, to state that pre-eclampsia or hypertension occurred in 11 % of pregnancies among previous kidney donors as opposed to 5 % of pregnancies in non-donors could be of more value to a potential donor than to say that there was "slight increase in the risk of pre-eclampsia".
8. Remain accessible	Donors who are under evaluation may benefit from having contact details for someone at the transplant centre who can answer questions as they arise during the evaluation process.
9. Educate transplant professionals in risk communication	Most transplant professionals know or have easy access to medical information on the short- and long-term risks that donors are facing. However, they may not necessarily have any formal education in how to communicate risks, or how to participate in shared decision making.
10. Relative *v.* absolute risks	For rare outcomes such as end-stage renal disease in previous kidney donors, a high relative risk could translate into a low absolute risk. However, this does not apply to more common outcomes.
11. Acknowledge uncertainties	Communicate to donors the degree of uncertainty associated with different risk estimates. This is especially important in younger donors.
12. Be neutral	The donor is the one making the decision whether to donate an organ or not. The role of the transplant professional is to provide neutral and clear information.

13. Young (< 30-40 years) donors are a special group	Long-term risk after donation is likely to be proportional to the remaining lifespan of the donor. Current studies on living organ donors are limited in follow-up time, making extrapolation of study results on behalf of young donors more uncertain than for middle-aged or older donors. Finally, most diseases will appear during middle age, making a normal donor evaluation in a young donor less reassuring than a normal donor evaluation in a middle-aged or older donor. This should all be taken into account when informing young donors.
14. Try to tailor information according to demographic group	Certain demographic or ethnic minority groups may be at increased risk after donation as compared to other groups. These people should receive information taking this into account.
15. There should always be an opportunity to stop the evaluation	Let the potential donor understand that they may change their mind regarding donation at any time, that the evaluation process will be stopped accordingly and that the transplant programme will assist in communicating the decision to the intended recipient.

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