George Galea · Marc Turner ·
Sharon Zahra · *Editors*

Essentials of Tissue and Cells Banking

Second Edition

Springer

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Preface

The 1st edition of this book has been very useful, in that it provided a concise and up-to-date information on the principles and scientific basis of tissue banking. Ten years have passed since its publication, and it was felt that an update was required.

Two important changes have been made to the previous edition. The first was a significant update on the all chapters. In some cases, the authors who had contributed before were asked to update their chapter to take into account of developments that have taken place in the intervening 10 years. In other instances, chapters have been written by different authors, who are recognized current experts in the field about which they wrote. All authors were given the same remit—to write succinctly and clearly on their chosen topic and to focus on current practices.

The second important change was a limited expansion into cell therapy. Many tissue establishments have developed processes that allow them to perform limited cellular therapy work. It was therefore felt that along with cord blood banking, haematopoietic stem cell processing should also be included. These are minimally manipulated cells that are now routinely banked.

It was very tempting to include a range of cellular therapies which are increasingly being handled; however, the techniques used in these areas such as culturing methodologies, measuring various cell markers, modifying them through gene therapy and producing advanced therapeutic medicinal products (ATMPs) are very different processes from the essentials of tissue banking that this book is meant to cover. Moreover, the target audiences of tissue and cellular banking are still broadly different although some convergence is beginning to take place, in that cells that are minimally manipulated are frequently handled by tissue establishments.

It may be that there will be more convergence in the future between tissue banking and cellular therapy and advanced therapeutic modalities. If that happens, it would make sense to combine the scientific principles covering all the available techniques into one book. I do not believe we are there yet, and the remit of this work would then diverge significantly from its original purpose. However, it was considered wise to add a chapter on the development of human embryonic cell banking. This was deliberately chosen to exemplify the complexities that banking such cells can provide and to illustrate the real differences between tissue banking and complexly manipulated cells.

I am grateful to two colleagues of mine Dr. Sharon Zahra and Prof. Marc Turner (both from the Scottish National Blood Transfusion Service and the University of Edinburgh) who helped me with identifying new experts to contribute to this edition and for supporting me in finalising this book. They were also very helpful in numerous discussions that took place throughout this book's gestation. I am also very grateful to all the authors who willingly gave their time and put much effort into this endeavour. Without exception, they wrote an up-to-date chapter in their area of expertise in a succinct and clear way.

There are now a number of universities and professional bodies that provide specific courses leading to a diploma or degree in tissue and cell banking. I believe that scientists, professional and medical staff working and wanting to develop their career in this field would find this book very useful. I believe it will also have a lot of relevance to clinical staff who use many of the products described in this book.

I believe therefore that this book should find a place on the shelf of many tissue establishments and who knows, in future years, there may be a third and future editions! I hope that the readers will find this book useful and as enjoyable as it was for me, editing and contributing to it.

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Contents

Live Donors of Tissue

1

Akila Chandrasekar

Abstract

Tissue transplantation is one of the recognized treatment strategies for replacing or repairing tissue damage resulting from disease or trauma. A living donor undergoing a surgical procedure can donate the surgical residues, such as femoral head, or placenta for amniotic membrane. Patients undoing solid organ cardiac transplantation can donate their own hearts removed for heart valve banking. Femoral head donated by patients undergoing primary hip replacement is the most widely and commonly banked tissue from living donors and is used in orthopaedic (spine and joint surgery) and oral/maxilliofacial surgery. Tissue donation to transplantation is a multistep process each of which is crucial to ensure safety and quality of the graft. There are many advantages of obtaining tissues from a living donor from tissue banking perspective. From donor selection perspective, the potential for self-exclusion and direct interview with the donor themselves to gather medical and behavioral history enhances the quality of information obtained. The blood tests can be performed on fresh, good quality samples rather than post-mortem samples as is often the case with deceased donors. Tissue is procured in a clean operating theatre environment under aseptic conditions, reducing the risk of contamination. The hospitals play key role in providing donations as well as users transplanting the tissues thereby living donor programme is a collaborative process between a tissue bank and these hospitals.

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1.1 Introduction

Human tissues and cells used in transplantation can be obtained from living or deceased donors. Some tissues and cells such as Haematopoietic Progenitor Cells (HPC) can only be obtained from living donors. Depending on the clinical circumstances, living donors donate tissues and cells for autologous use, where donation is collected for the patient's own treatment, or for allogeneic use, where tissues and cells are donated by a related or unrelated individual for the treatment of another person. HPC donations including Peripheral Blood Stem Cells, Bone Marrow and Cord Blood donations, and tissues consented and donated by living tissue donors for research and non-clinical use are excluded from the remit of this chapter.

A living donor undergoing a surgical procedure can donate the surgical residues, such as femoral head, or placenta for amniotic membrane, to be processed and stored as tissue grafts for allogeneic use. Patients undergoing solid organ cardiac transplantation can donate their own heart valves, derived from the heart that is removed during the procedure, to a heart valve bank if there are no medical contraindications to donation. In some cases, tissues from a patient can be processed and stored for autologous transplantation in the future, for example calvarial flaps removed during a decompression craniotomy. This chapter provides overview of altruistic tissue donation from voluntary unrelated living donors. Types of living tissue donations are summarised in Table 1.1.

Femoral head bone allograft is the most widely and commonly banked tissue from living donors and is used in mainly in orthopaedic (spine and joint surgery) and also in oral/maxilliofacial surgery. Amniotic membrane is used in the UK mostly in ophthalmic surgery as a biological dressing [1] but is sometimes used elsewhere as a skin substitute for management of burn wounds (as a temporary or permanent wound dressing) or to treat skin lesions such as vascular ulcers, epidermolysis bullosa or radiation burns.

1.2 Regulation

In the UK, the primary legislation covering tissue donation is the Human Tissue Act (2004) in England, Wales and Northern Ireland and Human Tissue Act (2006) in Scotland. The European Union Tissues and Cells Directives (EUTCD) comprising of the parent directive (2004/23/EC) [2] and the two associated technical directives were fully implemented into UK law via Human Tissue Safety and Quality (for human application) Regulations 2007. The regulatory body, the Human Tissue Authority (HTA), has the legal responsibility to license and inspect all establishments procuring and storing human tissue.

Table 1.1 Tissues donated by living donors

Tissue	Donor source	Operation	Donor interview staff	Procurement staff
Bone	Patients with osteo arthritis of the hip requiring hip joint replacement	Hip replacement with a prosthetic joint	• Tissue establishment staff • Hospital staff from the surgical team under a formal contract with the tissue establishment	Surgeons in operating theatre
Amniotic membrane	Mothers at the time of delivery	Elective caesarean section	• Tissue establishment staff Hospital staff based on a formal agreement • Between the tissue facility and hospital staff	Midwifery and obstetric staff
Heart valve	Patients undergoing heart lung block transplantation for cystic fibrosis where the heart may be unaffected	Explanted heart may be used as a source of heart valves	Tissue establishment staff Under contract with surgical team according to a clearly defined specification	Heart, heart/lung • Procured at time of explanation prior to heart lung transplant

1.3 Donor Identification

The banking of tissues for therapeutic use is a multi-step process, each of which is crucial to ensure safety and quality of the graft. The first step in that process involves identification and consent of medically suitable donors.

1.3.1 Femoral Head Donation

In the case of femoral head donations, potential donors may be identified in the out-patient department when they attend for surgical and medical assessment prior to their surgery. For those hospitals which run preoperative assessment clinics, this may be an ideal time to approach potential donors, when they are counselled about their forthcoming operation. They can be asked whether they are interested in donating the femoral head which otherwise would be discarded. At this time they will not be receiving pre-operative medication or receiving post-operative analgesia and therefore they should be able to make an informed decision, unclouded by

medication. Donors should be provided with information leaflets including information on medical contraindications, testing for microbiological markers, and the potential clinical use so that donors can self-exclude from donating if they have any risk factors or high risk behaviours that are contraindications to tissue donation. They should be reassured that their decision would not influence their surgical procedure or its timing.

1.3.2 Amniotic Membrane Donation

In the case of amniotic membrane, the information leaflets can be made available at the antenatal clinics to provide information on the process from donor selection, medical and behavioural history exclusion, the need of microbiological testing and the information about use of the donation. Information about potential donors may be obtained from the hospital through the obstetric lists of elective caesarean section deliveries to allow time to have a pre-consent discussion with the donor by trained healthcare professionals before commencement of labour, and for consent for collection to be given or declined before delivery.

1.4 Consent

The Human Tissue Act makes consent (authorisation in Scotland) the fundamental guiding principle covering the use of donated tissue for any purpose, and provides for financial and custodial penalties for breaches of its requirements. The HTA provides guidance and direction, through the publication of Codes of Practice, the first of which deals specifically with consent [3].

Donation of tissues must take place only after the person concerned has given free, informed and specific consent. For consent to be considered valid, it is important, that the person giving consent is fully informed with regard to all aspects of the donation process, including how, where and when the donation will take place, how much tissue will be removed, and the purposes for which the tissue may be used. With an adult living donor, the consent is taken generally from the donor themselves. Consent should be recorded and/or documented in the donor/patient's record. Informed consent must be discussed with the donor or their legal representative in a language and using terms they can understand. Records should confirm that the prospective donor and, where appropriate their legal representatives, has understood the information given, had the opportunity to ask questions and received satisfactory answers, before confirming their position regarding donation.

There are many models for obtaining consent from living tissue donors. They may be interviewed face-to-face by tissue establishment staff or by trained hospital staff working according to specified procedures. Hospital staff may be contracted to the tissue establishment and trained to use formal questionnaires, agreed in advance

and regularly updated using a document control system within a quality management system. The potential donors may be interviewed by telephone, by arrangement and with their prior consent, using the same questionnaire where the interview is documented using digital recording and where the telephone discussion becomes part of their donor record. The advantages of the latter model are considerable: the interview can be at a convenient time chosen by the donor in advance, the recording can be audited and used as a training tool, and not only is the consent recorded, but also the prior information provided to the donor. However, such a system does require resource and infrastructure to support it. All methodologies which are employed must ensure confidentiality, and the timing of the interview must consider donor competency issues, avoid the risk that the donor may be under the effects of medication, and consider any language comprehension issues.

Patients need to be informed that, if they consent to make a bone/amnion donation, it will require that they give permission to be tested for microbiology markers for infection which, in the UK, includes hepatitis B and C, HIV, HTLV1 &II and syphilis, and that where the results are pertinent to their health that they will be informed of those results and be advised how they should be managed. There may be additional discretionary microbiological tests such as for malaria or Chagas' disease if the donor's travel history indicates the need for this. Patients also need to be told that, in those tissue establishments where Nucleic Acid Testing (NAT) is not used to screen HIV/HBV/HCV on the blood sample taken at the time of donation, they would need to provide another follow up blood sample 6 months after the donation as well as one at the time of donation or very near to their operation [4]. Potential donors need to know that a comprehensive medical and behavioural history is needed to assess the suitability of the individual as a donor. The history taking is relatively time consuming and individuals should ideally be informed that all the questions are asked of every potential donor. They also need to be informed that donations unsuitable for therapeutic use may still be suitable for research and development. Research may be in the public sector where the outcome of research using donations of tissue may be published. Development work within the tissue establishment can lead to improvements in processing or other aspects of tissue bank procedures. Research may also be possible in the commercial domain, including for drug discovery work, although this would not benefit the donor financially. Donors should be also given the option to donate tissues for clinical use but decline consent for non-clinical use, with the understanding that if their donation is unsuitable for clinical use it will be discarded if they have not consented for research. For those donors who agree to allow donation a blood sample is commonly taken at the time of anaesthesia prior to the hip replacement operation. If a follow up sample is required (where the first sample is not NAT tested), this may be taken by the community doctor (primary care practitioner) 6 months post donation, then posted back to the testing laboratory or tissue facility. Patients who make donations need to be informed that the process of donor selection and testing mean that not all donations can be used therapeutically.

1.5 Donor Selection: Evidence Base and General Considerations

Transmissions of disease by tissue transplant, though rare, is well documented [5, 6] and includes examples of both infectious disease transmission and non-infectious disease transmission such as malignancy. The probability of blood-borne virus in tissue donors in the US has been documented [7] and although prevalence rates were lower than in the general population, they were higher than among first time blood donors. Brant found that the prevalence of infection is low among English tissue donors, but the risk was higher than that among new blood donors [8]. Safety measures for avoiding disease transmission to the tissue or cell recipient include careful selection of the donor, testing the donor for blood-borne infections, preventing contamination of the donation at procurement, processing [9] or storage and, where possible, disinfection or sterilization of the donated tissue prior to transplantation. This chapter mainly addresses aspects of donor selection.

The EUCTD [10] requires that adverse events and reactions are reported to the respective Member States' Competent Authorities. In addition to these vigilance and surveillance programmes, there are other useful resources such as the Notify Library [11] which is a publicly accessible database holding a collection and review of information from published literature. There are published reports of transmission of HTLV [12], HIV [13] and HCV [14] via frozen femoral heads from living bone donors. These donors were not tested at the time of donation as they donated prior to routine screening being introduced.

Considering tissues donated are stored for long periods before transplantation, the implications of changes to the donor selection criteria for tissue and cells to those grafts already in inventory, selected according to obsolete donor selection and testing, needs to be considered by tissue establishments in their policies concerning review of stock inventory. Such policies can usefully include a risk assessment-based approach on how to handle changes in selection criteria, and their impact on donations already in inventory.

1.6 Generic Contraindications

The main objective of donor selection procedures for living surgical tissue donors is to protect recipients without compromising the quality and sufficiency of the grafts to meet clinical demand. The major donor exclusion criteria for living tissue donors are:

1.6.1 Transmissible Infections

Potential donors with clinical or laboratory evidence of (have tested positive for) HIV, HCV, HBV or HTLV I/II infection at the time of donation must be excluded from tissue donation [4]. The tissue establishment should develop donor selection policies after considering epidemiological data on transmissible blood borne infections, the sensitivity and specificity of screening tests used for detecting these infections and the risk of undetected infection (window period) transmissions. Nucleic acid testing (NAT) can detect infection at a much earlier stage than the equivalent antibody test thereby reducing the "window period" where undetected infectious agents could potentially be transmitted. Many international guidelines recommend an interval of at least twice the window period since the last "at risk behaviour" for the length of deferral before donation. The deferral period would be longer if NAT is not done on donation sample [15].

Tissue donors are closely questioned about their behaviour to assess the risk of carriage of these blood borne viruses. Questions include whether an individual has had exposure through lifestyles which are associated with a higher incidence of certain infections than other sectors of the community. The risk associated with Men who have had Sex with Men (known as MSM) is higher with regards to blood-borne viruses like HIV than the general population [16]. Lifestyle risks include non-prescription drug taking, having sex in exchange for money or drugs, and, tattooing and body piercing done in settings not approved by the authorities. There are many countries which require some type of registration of tattoo parlours or acupuncture facilities and/or personnel and that makes it easier to exclude potential donors who have had procedures in non-registered facilities where the chance of re-use of needles or tattoo ink cannot be excluded.

It is a regulatory requirement that the antibody screening for HIV, HCV and HBV to be repeated in a second blood sample obtained from living tissue donors at least six months after the donation if NAT is not done on the donation sample when tissues are stored for long periods. The repeat negative result will ensure that there was no seroconversion and the first negative result on the donation sample was not in the window period.

If NAT is done on all donations, 3 months deferral of donors after potential exposure, for example if the donor is a sexual partner of a high risk individual, is acceptable [17]. Habitual drug users have additional risk of other infections that are not screened for and hence a longer period of exclusion of minimum 12 months is necessary for these donors [17]. The UK Blood Services Live Tissue Donor Selection Guidelines [18] and Guidelines for the UK Blood Transfusion Services [19] are available from the Joint Professional Advisory Committee for all tissue banks including non-blood service tissue banks.

1.6.2 Acute Infections

To minimize the risk of donor derived infections, donors with evidence of infection at the time of donation must be deferred and efforts should be taken to reduce the risk of contamination during processing. For amnion donors, maternal puerperal pyrexia or prolonged rupture of the membranes may point to a risk of bacterial infection, as might infants with possible congenital bacterial infection associated with amnionitis.

1.6.3 Risk of Transmission of Prion Diseases

It is unlikely people diagnosed with Creutzfeldt–Jakob disease (CJD), or variant Creutzfeldt-Jacob disease (vCJD) or those with a history of rapid progressive dementia or degenerative neurological disease would be considered for an elective surgery or considered fit to donate tissues or cells. In addition, the following risks must be considered [18].

(a) Living donors with a family history of non-iatrogenic CJD
(b) Recipients of hormones derived from the human pituitary gland (such as growth hormones) and recipients of grafts of cornea, sclera and dura mater, and persons that have undergone neurosurgery in the past (where dura mater allograft may have been used, but not documented).

For vCJD, further precautionary measures recommended in the UK include exclusion of blood transfusion recipients and individuals who have been told that they may be at increased risk (because a recipient of blood or tissues that they have donated has developed a prion related disorder) from donating blood and tissues.

1.6.4 Malignancy

Whilst transmission of malignancy is well documented for organs, the risk of transmission of malignant disease from tissues is very low, with no reported transmission of malignancy through bone allografts. The Commission Directive, 2006/17/EC [4] requires that malignancy, with a few exceptions, be considered a contraindication to donation. A survey published in 2006 [20] showed that the commonest exclusions from femoral head donors are reported to be pre-existing bone or joint conditions and malignancy. The reported exclusions of donors of femoral heads for "malignancy" represent active malignant disease and non-metastatic disease or individuals in remission for some years. On the other hand, some donors with no reported history of malignancy may have occult malignant disease, sometimes detectable in donated bone. Cases of low grade lymphoma were revealed in retrieved bone allografts [21] and evidence of malignant lymphoma and low grade chondrosarcoma were found in femoral heads

otherwise considered suitable for donation [22]. However, it can be argued that donor acceptance and deferral criteria should be risk assessed based on evidence of transmissibility. Processing of tissues to remove donor cells may be a valid means of accepting donations from individuals with a history of malignancy not affecting the specific tissue to be retrieved. Donor and recipient histo-incompatibility, plus recipient immune competence further reduce the chance of survival of malignant clones in the recipient and, together with the removal of oncogenic viruses, means that deferral for malignancy for bone donation could be reviewed on the basis of these combined factors. A firm evidence base is needed if standards for exclusion are to be effective in ensuring quality and safety of donated tissue, whilst preventing arbitrary exclusion of some tissue donors.

1.7 Retrieval/Procurement

Once suitable donors are consented, the next step is to retrieve or procure the donation. In living tissue donors this is done at the time of hip replacement surgery, for bone donation, or at the time of delivery for amnion.

In the operating theatres a member of staff trained in the procurement of bone will have responsibility for holding and maintaining a stock of sterile packaged containers, supplied by the tissue establishment, to be used to contain the donated femoral head after it is removed by the surgeon. The surgeon may also remove an analyte validated to represent the donation, commonly bone chips from the femoral head, and place these into enrichment broth for aerobic and anaerobic bacteriology culture according to the requirements of the individual tissue establishment. All the documentation, bone containers and associated testing analytes, including bone chips for culture and blood samples for microbiology testing, must be labelled with a unique identifier to allow tracking from the donor, via processing and testing, to the recipient. Ideally the labelling technology used will be compatible with testing laboratory equipment so that manual transcription of information about the donor is avoided and computer traceability is ensured.

In the case of femoral head donation there is a need for extensive interaction between the tissue establishment and outpatient and theatre orthopaedic staff, with a need for training and audit, and updates to staff training.

Donation of amniotic membrane is in principle a very similar process. The amnion is collected at the delivery from mothers undergoing elective caesarian section, whereby the placenta is removed surgically under aseptic conditions, exposing it to less risk of contamination than a vaginal delivery. The whole placenta is collected and sent to the tissue establishment for further processing. Again there is a need for close co-operation between midwifery, obstetric out-patient and in-patient delivery suite staff.

1.8 Summary

Obtaining tissue from living donors has many advantages from a tissue banking perspective. Firstly, it is procured in a clean operating theatre environment by surgeons. As the tissue is taken from living donors under aseptic conditions, the risk that it may be contaminated is greatly reduced. From donor selection perspective, the potential for self-exclusion and direct interview with the donor themselves to gather medical and behavioural history enhances the quality of information obtained. Another advantage is that blood tests may be performed on fresh, good quality samples rather than post-mortem samples as is often the case with deceased donors.

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Deceased Tissue Donors

2

Sharon Zahra

Abstract

Tissue donation after death includes several different products which can be life-enhancing (such as tendons) or life-saving (such as heart valves), with an individual tissue donor being able to potentially help many different patients. Different to organ donation, tissue donation can take place up to several hours after death; this means that the number of potential tissue donors is much higher than that of organ donors, although careful attention to body cooling after death is required to ensure that the quality and safety of the tissue products is maintained. It is important to ensure that appropriate consent is in place prior to proceeding with tissue retrieval. Further, due to the nature of deceased donation, information provided at the time of donation as to the medical, behavioural and travel history of the donor is necessarily second hand, making it very important that all available information on the donor is reviewed and assessed (including speaking to the donor's family and family doctor, reviewing medical records and post-mortem as appropriate) to ensure a full risk–benefit assessment is carried out prior to releasing the donation for clinical use. Tissue retrieval requires well trained staff to ensure that the products are not damaged during the retrieval process; and finally due care and attention is required when taking blood samples for donor testing of mandatory markers of infection to ensure that the blood samples taken are truly representative of the donor's infectious disease status.

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2.1 Introduction

An individual deceased tissue donor can improve and even save the life of many different patients. While tissue donations are essential for several routinely available surgical procedures e.g. cruciate ligament repair following knee trauma or repair of congenital heart defects, tissue donation is much less well recognised and understood than organ donation, the latter having a much higher profile with the general public and even medical professionals. This despite the fact that the number of potential tissue donors is likely to be far higher than the number of organ donors, and that a single tissue donor may be able to help numerous recipients.

The potential for tissue donation after death is ever increasing and currently includes the potential to donate corneas, tendons, bone, pericardium, blood vessels, cartilage, heart valves and skin. Tissue donors can also be organ donors; indeed some donors are able to donate both organs and tissues, and some donors who start off on the organ donation pathway but end up not being able to donate organs for any reason (e.g. time from cessation of supportive care to confirmation of circulatory death being too long for successful organ donation) may yet be able to donate some or all tissue products.

Organ versus Tissue Donation

While organ donation and transplantation tends to be immediately life-saving e.g. liver transplant in the setting of acute liver failure, most tissue products tend to be life-enhancing (although some tissue donations, e.g. heart valves, may be life saving). In view of this the risk/benefit assessment carried out when deciding on the suitability or otherwise of a potential tissue donor is different to that carried out when deciding on the suitability or otherwise of a potential organ donor; for example higher risk donors (e.g. evidence of chaotic lifestyle, illicit drug taking) are usually considered unsuitable for tissue donation.

Despite this the number of suitable potential tissue donors is higher than that of suitable organ donors due to the need to maintain metabolic function in organ donation as different to tissue donation. Indeed for organ donation to be possible the potential donor needs to die in hospital, most often in an intensive care unit, with retrieval surgeons able to mobilise for retrieval as soon as possible after the confirmation of death to ensure that the retrieved organs retain their metabolic function. On the other hand, compared to organ donation, tissue donation can take place at a later timepoint from the time of death. While it is important to maintain the structural integrity and sterility of tissue donations, there is no need to maintain metabolic function of living cells in most tissue donations; this means that tissue donation is possible in a larger number of deaths.

A further important difference between organ and tissue donations is that at present, donated organs need to be transplanted as soon as possible with no current possibility of prolonged storage. This is not the case with tissue donation, where donations have a “shelf-life” i.e. they can be stored for prolonged periods of time—at the longest up to 10 years for cryopreserved heart valves, with variable storage

periods for other tissue donations [1]. This ability to store donations before clinical use makes it possible to carry out a more detailed risk/benefit assessment before releasing tissue donations for clinical use, as compared to organ donations.

2.2 Deceased Tissue Donor Identification

A successful deceased tissue donation programme requires an established system for referral of potential deceased donors from the place of death to the retrieval service.

It is important to engage effectively and regularly with all areas where deceased tissue donors may be referred from. Given tissue donation can take place several hours after death, potential tissue donors can be referred from any place where a potential donor has died, including clinical areas within hospitals, hospices, funeral homes and even the potential donor's own family home.

Different to blood donation, where the volunteer healthy donor makes a personal decision to attend for donation on a given day, tissue donation after death can only take place if there is a well established referral system in place so that the potential of donation is routinely considered as part of the end of life care of an individual. With good engagement with clinical areas, it is possible to set up a system where a formal decision is taken at each and every death as to whether tissue donation is possible or not, and thus the potential donor referred on to the tissue donation service where appropriate.

Clinical areas are often very busy, such that facilitating donation after an individual's death may be seen as an extra responsibility that is getting in the way of managing living patients. However the management of some of these patients is dependent on tissue donation. Having a well established system such that the possibility of tissue donation is considered at each and every death is important to avoid missing donation potential. Providing the clinical areas with teaching about the potential of tissue donation and an easy to refer to list of the main reasons that would make an individual unsuitable for tissue donation (e.g. presence of certain infections) would allow effective decision making at the time of a patient's death on whether to refer a potential donor or not.

It is equally important to raise awareness about the potential of tissue donation with the general public. Given many organ donors can also be tissue donors, and vice versa, it is important to provide the general public with information about the potential of both organ and tissue donation after death. By regularly discussing the possibility of donation, and providing information as to why such donations are important, tissue (and organ) donations become the norm within a society, something that can be openly discussed from a young age. This means that the general public is already aware of the possibility of tissue donation, making the conversation at the time of a loved one's untimely death much easier to approach and also increasing the chance of a positive response from the family as tissue donation would be a subject that they are already aware of [2, 3].

In order to help ensure the safety of tissue donation it is important to continue to promote tissue donation from volunteer unpaid donors with no monetary incentive offered to their next of kin. It is equally important to protect the donors themselves by ensuring anonymity of the donor at all times to protect their personal privacy, even after their death.

2.3 The Law and the Role of the Family

Before tissue donation can be progressed from an individual it is important to confirm that legal consent is in place. Different countries manage consent for tissue (and organ) donation in different ways. Some countries, e.g. the United States of America, use an Opt-In system whereby individuals can make a decision in life as to whether they would like to be a tissue (and/or organ) donor at the time of their death. By deciding that they would like to be a tissue (and/or organ) donor they Opt-In to donation i.e. they register in life their decision that they would wish to be a donor at the time of their death. This decision can be registered in various ways: by adding one's name to a national Organ Donor Register, by carrying an Organ Donor Card, or by telling one's family about their decision or including it in a will.

On the other hand, other countries e.g. Spain operate an Opt-Out system for donation i.e. all individuals are considered to be potential donors at the time of their death unless an individual has registered a decision contrary to this i.e. not to be a donor. Again the decision to Opt-Out can be done in various ways including registering one's decision not to be a donor on a national register.

Both Opt-In and Opt-Out can be "hard" or "soft". Hard Opt-In/Out systems are ones where the individual's decision is final i.e. at the time of death this decision cannot be over-turned. A soft Opt-In/Out system on the other hand allows for the input of the next of kin to be taken into consideration at the time of an individual's death.

Both systems have their pros and cons. While a "hard" system would mean that the family would not be able to over-turn an individual's decision thus potentially increasing the number of successful donations, it is important to keep in mind that the family have an important role to play in deceased tissue donation. The family may have information that indicates that the potential donor had recently changed their decision regarding donation but had not had the opportunity to formally register their new decision. Further in deceased tissue donation the information required to assess the safety of the donation is by necessity second hand, usually from family members of the individuals who knew the potential donor well. It is therefore very important that the family are engaged with the process at the time of donation to ensure that they provide all information that is required to assess the safety of the donation. Further while it is very important that tissue donation potential is maximised to be able to meet the clinical demand for such donations it is equally important to respect the grief of acutely bereaved families and to also avoid any potentially damaging media attention that may result if tissue donation

were to be progressed in the face of family opposition in cases where the individual had taken the decision in life that they would have liked to be a donor at the time of their death.

Further a family's refusal to agree to donation may be a warning of potential high-risk behaviour—some families may prefer to say they do not wish donation to take place rather than providing highly personal and sometime embarrassing information about the donor in response to the sometimes probing questions that are asked of all donor families. It is therefore important to sensitively engage with the family; in the face of refusal, proceeding at all costs is unlikely to be sensible and should be discouraged. Trying to understand the family's reason for refusal would be important to reach the right decision for that donor and their family both on a personal level and to ensure the safety of the donation [4, 5].

2.4 Age Cut-Offs

The types of tissue donation progressed from an individual donor varies according to the donor age. Some of the age limits applied for tissue donation are relatively empirical, and indeed different tissue banks apply different age cut offs for the same type of tissue donation. The age limits recommended for a number of tissue types donated quoted in this section are based on the JPAC UK guidelines [6], which provide generic guidance on the recommended age limits for the different types of tissue donation. These age limits can of course be varied if a tissue bank can demonstrate that a particular tissue remains suitable for transplantation at older age limits.

When considering heart valve donation it is important to note that most heart valve donors are adults while most heart valve recipients are young children. When deciding to use a particular valve for an individual patient important considerations include the diameter of the valve as well as the length of vessel retained with the valve. The UK guidelines recommend heart valve donation from as young as 32 weeks gestation, up to 70 years of age. As individuals get older the effect of hypertension/cardiovascular disease are most pronounced on the aortic valve with a much lesser effect on the pulmonary valve. Indeed a significant proportion of aortic valves from donors above 60 years of age are found to be unsuitable for clinical use due to the presence of calcification or other age-related changes while pulmonary valves are often still in good condition up to and including 70 years of age.

The UK guidelines recommend that tendon donation can be progressed from donors between 17 and 60 years of age, the upper age limit to minimise the risk of wear and tear in the tendon from increasing age.

There is no upper age limit for skin donation—as long as the skin appears normal and not too thin (a consideration in older donors) then skin donation can be progressed. It is important to ensure that the donated skin is free of skin lesions and tattoos. The UK guidelines recommend an upper age limit of 70 years similar to heart valves, mainly as it not cost-effective to progress skin only donation in older donors. When considering progressing skin donation a consideration is the size of

the donor—the yield of skin from smaller donors is unlikely to be sufficient to be clinically effective.

The current UK age guidelines for cornea donation are 2–95 years of age. In reality if the cornea is clear cornea donation is likely to be suitable.

For bone donation the current recommended age limits are 17 to 50 years for structural bone donation, while there is no upper age limit for non-structural bone donations.

2.5 Medical, Behavioural and Social Assessment

All tissue donors are tested for the potential presence of a number of blood borne infections; mandatory testing within Europe at present includes serological testing for the presence of HIV, hepatitis B, hepatitis C and syphilis, and where indicated HTLV [7]. However, despite this mandatory testing for the main transplant transmitted infections, donor assessment to assess the risk of transmission of infection remains important, partly due to the possibility of false negative results in any assay carried out and partly due to the possibility of new emergent infections, the risk of which may (although not necessarily so) be reduced by deferring potential donors who are identified as showing high-risk behaviours. Further there are some current infections, namely prion related conditions, that cannot be screened for.

Donor assessment is also important to assess the risk of transmitting diseases other than infection, the main condition being the risk of transmitting cancer from donors with undiagnosed cancer at the time of their death.

While not ideal, and considered by most a blunt tool, donor medical, travel and behavioural questionnaires looking for the potential presence of infection or disease that could negatively affect the suitability of tissue donation therefore remain an important tool in ensuring the safety of tissue donations. In the setting of tissue donation after death the information obtained is always second hand from the next of kin (who knew the potential donor best), to the best of their knowledge. In view of this the number of questions used to elicit the medical, travel and behavioural history are numerous to try and gather as complete a picture as possible. When reviewing the information provided, it is important to be mindful that the information provided is second hand and may therefore be inaccurate, so that caution needs to be exercised when deciding whether to release a donation for transplant or not particularly in the setting of incomplete information being available or when contradictory information has been provided. It is also important that the person who is best placed to answer the different questions is approached—for example in the case of an adult donor, while the available next of kin may be the donor's parents, the parents may not be best placed to answer social and behavioural questions if the donor also had a partner or friends who were better placed to answer questions about the potential of drug taking or sexual contact for example.

It is important to ensure that all relevant information about a particular potential donor is obtained and reviewed, including the details of their last hospital admission (if relevant) prior to donation. This will involve reviewing the medical notes, in

particular looking for findings that would suggest untreated infection being present or red flag symptoms that may suggest the presence of an undiagnosed condition at the time of the donor's death such as symptoms suggestive of prion disease or underlying malignancy.

Prior to proceeding with tissue (or organ) donation an external body examination must be carried out as a further donor check looking specifically for findings that may suggest underlying infection or significant disease that could adversely impact on the safety of the donated tissue, in particular looking for the potential of track marks, fresh tattoos or body piercings, unexplained rashes, evidence of malignancy, evidence of infection etc. (refer to Annex IV of Commission Directive 2006/17/EC: https://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2006:038:0040:0052:EN:PDF [7]). This external body check provides further support for the safety of the proposed donation. Any unexpected findings need to be investigated as necessary to ensure there are no conditions in the donor that would adversely impact the safety of their donation.

If the tissue donor is also an organ donor, organ retrieval surgeons will carry out a visual inspection of all internal organs at the time of retrieval. Their findings must be documented in the donor's medical notes and any unexpected findings, e.g. previously unidentified lesions that could be cancerous, communicated with any tissue banks who are planning on retrieving tissue from the donor as this may impact the suitability or otherwise of the proposed donation. In fact in the case of organ donors the examination at the time of organ retrieval is akin to a post-mortem examination and may lead to important findings that could impact the safety of donation.

Some tissue donors will also have a post-mortem carried out after donation—usually in the case of donors who die unexpectedly or in suspicious circumstances. In such cases it is important that the tissue bank reviews the findings of the post-mortem prior to releasing any of the donations for transplant as such post-mortems may again identify a previously unidentified condition that may mean donation is not safe from that donor e.g. evidence of malignancy or infection.

Due to the importance of ensuring as complete a picture as possible about the medical and behavioural history of the deceased donor it is also important to ask for information from the donor's family doctor who may have information that the next of kin may not be aware of; example if the donor was only recently attending for investigation of new symptoms or had previously required treatment for infections that the donor may not have told his next of kin about.

When deciding on the suitability (or otherwise) of tissue donation from a particular tissue donor a risk/benefit assessment needs to be carried out in each and every case, taking into consideration all the information gathered from the various different avenues i.e. next of kin, hospital notes, family doctor, donor examination prior to tissue retrieval (and/or at organ retrieval) and post-mortem (if carried out). Caution needs to be taken when the information appears incomplete or contradictory. Due to the fact that donated tissue can be stored for extended periods of time there is sufficient time to obtain detailed information from a number of sources as described to ensure the safety of the donation.

The EU Directive [7] on the quality and safety of tissue donation provides broad guidance about the conditions that need to be excluded to ensure the safety of donation (specifically refer to Annex I of Commission Directive 2006/17/EC: https://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2006:038:0040:0052:EN:PDF). This Directive has been incorporated into national law in the various EU member states. Locally available national guidelines are available in most countries translating the EU Directive into professional guidance on what conditions would raise concern about the safety of donation and vice versa. In the UK deceased donor selection guidelines can be found on the publicly available website of the Joint United Kingdom Blood Transfusion and Tissue Transplantation Services [8]. These detailed guidelines aim to provide generic guidance to help ensure that tissue donor assessment is carried out consistently.

It is worth noting that the risk of disease transmission through cornea donation is different to that of other types of tissue donation, due to the fact that the cornea is avascular. Indeed while a history of malignancy is considered a contraindication for most types of tissue donation, the presence of most types of solid cancers (either current or historical) would not necessarily be a contraindication to cornea donation, although haematological cancers and cancers of the eye would still lead be a contraindication to cornea donation. The UK guidelines [8] indeed provide separate guidance on the suitability of cornea donation as different to other vascular tissues.

2.6 Blood Sampling and Haemodilution

The EU Directive on the quality and safety of tissue donation [7] (specifically refer to Annex II of Commission Directive 2006/17/EC: https://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2006:038:0040:0052:EN:PDF) defines the mandatory minimum testing that needs to be carried out on each tissue donor to minimise the risk of transplant transmitted infection. For deceased donors the mandatory testing for blood borne infection includes serological testing for HIV, hepatitis B, hepatitis C and syphilis. HTLV testing is also indicated if the donor, their sexual partner or their parents lived, or originated from, high-HTLV incidence areas.

Individual tissue banks often carry out more extensive testing than the minimum testing required by law. Most European tissue banks also do NAT testing for HIV, hepatitis B and hepatitis C. The UK also tests all donors for HTLV irrespective of their country of origin and has recently also started to do HEV NAT testing.

Additional testing for the possibility of the presence of other infections may also be indicated based on the donor's history, in particular their travel history—for example testing for West Nile Virus, malaria and other tropical viruses depending on the destination and timing of any travel.

When taking blood samples for blood borne infection testing it is important to consider the timing of blood sampling and the possibility of haemodilution . Due to the changes that happen in the blood after death it is preferable for blood sampling

to take place as close to the time of death as possible, and if possible before circulation ceases, to ensure reliable results. If the latter is not possible then blood samples must be taken within 24 h of death to minimise the risk of both false positive and false negative results [7].

In donors who have had blood loss and transfusion/infusion of colloids or crystalloids it is also important to consider the potential of haemodilution leading to false negative results particularly in donors who may have low levels of antibodies. The risk of missing HIV, hepatitis B and hepatitis C infection is reduced if also carrying out NAT testing, however before accepting the testing results it is important to consider the potential impact of haemodilution. As per the EU Directive [7] tissue establishments must validate the testing procedures used if wishing to accept blood samples (for blood borne infection testing) that are more than 50% haemodilute. The decision making process and the haemodilution algorithm currently used in the UK is shown below in Fig. 2.1a, b.

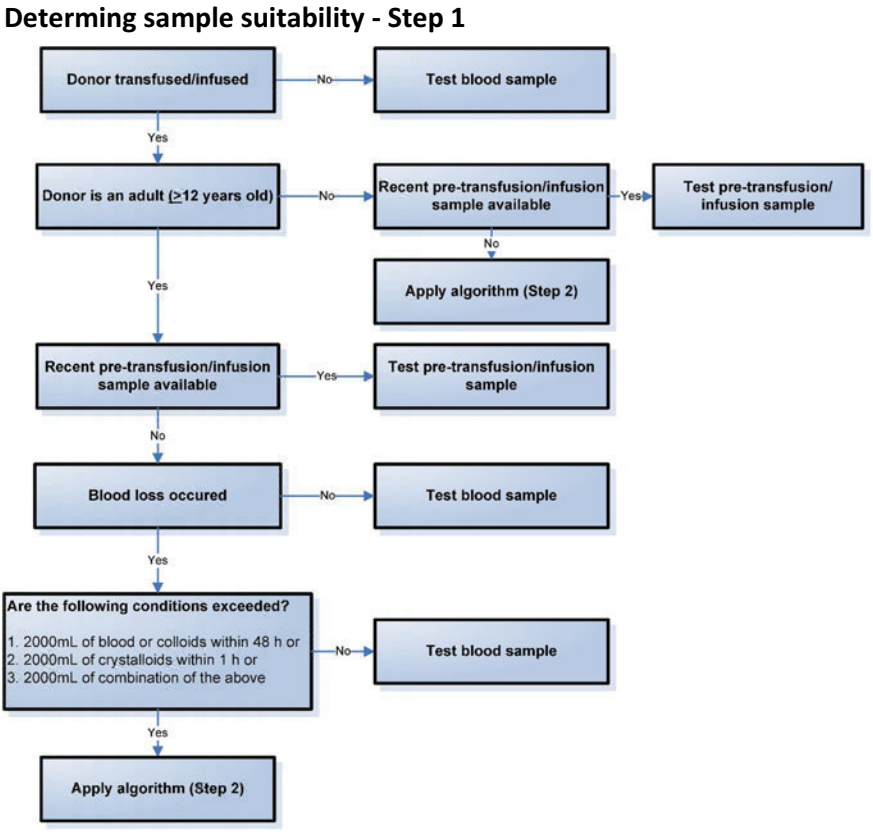

Fig. 2.1 **a** Flow chart to follow to determine whether a haemodilution calculation is required or not. **b** Haemodilution calculation currently in use in the UK

Determing sample suitability - Step 2

Donor ID:		Date & Time blood sample taken:	

Step 2A

Calculate plasma volume	Donor weight (kg) $\frac{\_\_\_\_\_}{0.025}$	_____mL
Calculate blood volume	Donor weight (kg) $\frac{\_\_\_\_\_}{0.015}$	_____mL
A) Record total volume of blood transfused in the **48 h** prior to death or sample collection (whichever comes first).	_____mL of RBC transfused/48 h _____mL of whole blood transfused/48 h _____mL of reconstituted blood/48 h	Sum A: _____mL
B) Record total volume of colloid infused in the **48 h** prior to death or sample collection (whichever comes first)	_____mL plasma/48 h _____mL platelets/48 h _____mL albumin/48 h _____mL HES or other colloids/48 h	Sum B: _____mL
C) Record total volume of crystalloid infused in the **1 h** prior to death or sample collection (whichever comes first)	_____mL	Sum C: _____mL

Step 2B

Calculated Plasma Volume	_____mL	Sum B + Sum C	_____mL	
Calculated Blood Volume	_____mL	Sum A + Sum B + Sum C	_____mL	
Calculate plasma dilution	Is Sum B + Sum C > plasma volume?		No	Yes
Calculate blood dilution	Is Sum A + Sum B + Sum C > blood volume?		No	Yes

If the answers to **both** questions are 'No', the post-transfusion/infusion sample is acceptable

If the answer to **either** of the questions is 'Yes' use a pre-transfusion/infusion sample. If a suitable sample is not available, seek expert advice and inform transplant centre, testing laboratory, tissue bank as necessary.

RBC = red blood cells; HES = hydroxyethyl starch

Fig. 2.1 (continued)

2.7 Timing and Venue of Retrieval

Different to organ donation, tissue donation can take place several hours after death. As previously mentioned in tissue donation there is no requirement to maintain metabolic function; instead the concerns with tissue donation is the structural integrity of the donation as well as minimising the risk of contamination from