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SaBTO

Advisory Committee on the Safety of Blood, Tissues and Organs

GUIDANCE ON THE MICROBIOLOGICAL SAFETY OF HUMAN ORGANS, TISSUES AND CELLS USED IN TRANSPLANTATION

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Contents

1. Introduction

1.1. This guidance updates and replaces the 'Guidance on the Microbiological Safety of Human Organs, Tissues and Cells used in Transplantation' issued in August 2000 by the Advisory Committee on the Microbiological Safety of Blood Tissues and Organs for Transplantation (MSBTO).

1.2. MSBTO was replaced by the Advisory Committee on the Safety of Blood Tissues and Organs (SaBTO) in 2008. SaBTO's role is to advise Ministers of the UK Government and the Devolved Administrations as well as UK Health Departments on the most appropriate ways to ensure the safety of blood, cells, tissues and organs for transfusion and transplantation. This includes reducing to a minimum the avoidable risk of transmission of infection through transplantation.

1.3. This guidance has been written by a working group (members are listed in Annex 1) after extensive consultation. Other publications on this subject were taken into consideration during the preparation of this document. Separate guidance is available on the transfusion of blood and blood products.

Scope

1.4. The guidance laid out in this document provides advice on ensuring the microbiological safety of human organs, tissues and cells used in transplantation. Table 1 contains a list of most of the organs, tissues and cells (haemopoietic, reproductive and other cells) covered by this guidance.

1.5. Reproductive cells, embryos and embryonic stem cells and haemopoietic stem cells are now within the remit of this guidance. However, the microbiological safety and quality of human blood and blood components, and the safety, quality and efficacy of blood products, is covered elsewhere.

1.6. The underlying principle running through this guidance is that the risk of an infection being passed on through transplanted organs, tissues and cells should be kept to a minimum, taking account of the balance of risk and benefit for the recipient. In urgent life-preserving situations, a higher risk of infection may be acceptable; stricter controls are needed in non-urgent situations and for transplants aimed at improving a patient's quality of life rather than saving it.

1.7. This broad principle also applies to the source human tissues and cells cultured in a laboratory before transplantation and to manufactured products or services that use human cells or tissues. Avoiding the transfer of malignant cells in transplanted organs, tissues and cells is also essential but is not covered by this guidance. Other potential physical and chemical risks which do not relate to micro-organisms are likewise not addressed here.

1.8. Where appropriate, this guidance follows many of the recommendations in place for the selection and microbiological testing of blood donors. However, we recognize that there are some situations particularly in urgent organ donation and transplantation, which are greatly influenced by the need to retain organ viability, where the testing of potential donors will be different and conducted under severe time constraints. In these situations, the testing that will need to be carried out, and the general principles for balancing the risks and benefits, are set out in this guidance. Tables 1 and 2 set out in broad terms the human materials covered, the types of donor, the types of donation and the time available for assessing a potential donor. Sections 8 and 9 set out the main recommendations covering microbiological screening of organ, tissue and cell donors together with resulting actions to take from the identification of

an infected (or potentially infected) donor. For organ donors and deceased tissue donors, the information requirements for assessing a donor's risk of harbouring an infection are set out in the NHS Blood and Transplant Patient Assessment Form (PA1) – current version is August 2009.

1.9. This is a developing area and the guidance reflects good practice in accordance with available evidence, supplemented by expert opinion where published evidence is lacking. This guidance acknowledges those areas that are contentious, and recognises that further work and debate are needed. The recommendations in this guidance need to be reviewed at a minimum of every three years and on a case by case basis should the need arise.

Table 1: Examples of human material covered by this guidance

Organs	Tissues and cells	Haemopoietic cells (HPC) and Therapeutic cells (TC)*	Reproductive cells	Human embryonic stem cells (hESCs)
Bowel Heart Kidney Liver Lung Pancreas Composite tissue transplants, e.g. face, hands Regenerated organs	Bone Cartilage Cornea/sclera Heart valves Skin Tendons Vascular tissue Amnion Menisci Pancreatic islet cells** Ocular stem cells, i.e. limbal*** Chondrocytes Keratinocytes*** Induced pluripotent stem cells (iPS)	Bone marrow stem cells (HPC-marrow) Peripheral blood stem cells (HPC-apheresis) Umbilical cord blood (HPC-cord blood) Donor lymphocyte infusions and other Therapeutic cells	Gametes (sperm and ova) Embryos created *in vitro* Immature ovarian or testicular tissue	Embryonic stem cell lines intended for clinical use derived from human *in vitro* fertilisation/ intracytoplasmic sperm injection procedures (not cryopreserved) Embryonic stem cell lines intended for clinical use derived from cryopreserved human embryos

* TCs include a wide range of selected and cultured products including T-cells, Natural killer cells, mesenchymal stem cells, cytotoxic T-lymphocytes, T-regulatory cells, tumour derived cells.

** Although islet cells are processed (isolated and purified) they are subject to time constraints akin to organs

*** Limbal stem cells, keratinocytes and embryonic stem cells are usually cultured and expanded in the laboratory and should be considered as tissues for the purposes of microbiological testing. Cells used as feeder layers at any stage in the process are considered to fall within this guidance and also require microbiological testing including for potential zoonotic infections where feeder cells are of non-human origin. In addition, some of these materials may also be considered advanced therapeutic medicinal products (ATMPs) and are therefore regulated by the appropriate guidelines. In addition, the statutory requirements set out in the Human Tissue (Quality and Safety for Human Application) Regulations 2007 still apply to the procurement, donor selection and testing of the starting tissue.

Legislation

1.10. We have endeavoured to align our advice in this guidance with the very extensive regulatory framework developing in this field, whilst remaining mindful of the clinical need for transplantation.

1.11. Since the last guidance was published, the European Union Tissue and Cells Directive[1] (EUTCD) has been transposed into UK law through the Human Tissue (Quality and Safety for Human Application) Regulations 2007, and through the Human Fertilisation and Embryology (Quality and Safety) Regulations 2007 which amended the Human Fertilisation and Embryology Act 1990 in 2008. The procurement, testing, preservation, storage and distribution of tissues and cells, including those for assisted conception, for human application are now regulated through the UK competent authorities, namely the Human Tissue Authority (HTA) and the Human Fertilisation and Embryology Authority (HFEA).

1.12. In May 2010, the European Parliament voted to pass legislation that would set common quality and safety standards for organ donation and transplantation across the EU. The Parliament also backed the Commission's 2009-2015 action plan on organ donation and transplantation. The proposal for a Directive and accompanying 10-point action plan were put forward by the Commission in December 2008, with the aim to help increase the supply of organ donors across the EU, enhance the efficiency and accessibility of transplantation systems and ensure the quality and safety of the procedures. The Directive (2010/53/EU) came into force in August 2010 and national governments have two years to transpose it into national legislation. The Directive requires EU member states to set up a Competent Authority or Authorities responsible for maintaining quality and safety standards for organs intended for transplantation. These authorities will approve procurement organisations and transplant centres, set up reporting and management systems for serious adverse reactions, collect data on the outcome of transplants and supervise organ exchanges with other member states and third countries.

1.13. In some respects the recommendations in this guidance may exceed the requirements of the statutory regulations, and in doing so are believed to reflect consensus views for good practice. This is particularly true for the development of genomic detection through molecular testing (NAT) testing which offers a significant advance in terms of both sensitivity and specificity but is not immediately accessible to many. Where possible its use should be considered and its introduction more widely for transplantation work is an aspirational development. Similarly, where newer protocols for testing can replace existing protocols and give operational advantages with no impact upon microbiological safety this has been addressed. Tissue establishments and transplant establishments receiving donations from outside the UK should as far as possible ensure that the donor testing meets the recommendations of these guidelines either at retrieval or on receipt in the UK.

[1] 2004/23/EC – Parent Directive; 2006/17/EC – First Technical Directive; 2006/86/EC – Second Technical Directive

2. Overview of the microbiological safety of transplantation

2.1. Transplantation has been one of the great success stories in health care. However, there have been repeated reports of transmissions of viruses, bacteria, fungi, protozoa and prions following transplantation of organs, tissues and cells. These transmissions can be difficult to manage as the recipients may be immunosuppressed and thus more susceptible to becoming ill from the infection. The risk of infection during the whole process of transplantation can never be completely removed. This guidance sets out precautions that should help to keep the risk as low as is reasonably possible whilst at the same time facilitating the maximum clinical benefit from transplantation.

2.2. Good transplantation programmes rely on teamwork. People from a range of specialist fields are involved in the selection of donors and in collecting, testing, processing, storing, transporting and transplanting organs, tissues and cells. They include surgeons, physicians, gynaecologists, specialist nurses, clinical microbiologists and tissue co-ordinators in hospitals, as well as laboratory staff and specialists working in tissue and cell establishments and assisted reproduction programmes. This guidance is for everybody involved in transplantation.

2.3. Transplants have many benefits, whether life-preserving (such as heart or HPC transplants) or life-producing procedures (such as in-vitro fertilisation – IVF), or those aimed at improving the quality of life (such as bone grafts). The risk of infection from a particular donor may be an absolute contra-indication to accepting a bone donation but only a relative contra-indication for liver donation where the potential recipient would otherwise die from liver failure. For this reason, the criteria used to accept a tissue donor can, and should, be stricter than those for organ donors. However, in all cases where unusual or extra risks of infection are identified with a particular possible donation, these should be discussed in detail with the person who would receive the organs, in the case of a child with their guardian, and/or their family where appropriate before transplantation. The discussion and the consent if given should be recorded in the patient's clinical notes. Specific treatment or prophylaxis of the recipient, and where necessary their partner(s), may be offered to mitigate risks.

2.4. Infection may also result from transplant material becoming contaminated from organisms in the environment. Contamination may occur while the material is being collected, processed, packed, tested, stored, transported and/or transplanted. Standard procedures for all these activities should include a microbiological risk assessment as part of a wide-ranging quality assurance programme.

2.5. The highest standards should be maintained when choosing donors and when collecting, processing, packing, testing, storing, transporting and transplanting organs, tissues or cells. Introducing and maintaining a recognised quality management programme (for example ISO 9001) will contribute significantly to the safety and quality of all types of graft used in transplantation. For establishments procuring or processing tissue intended for clinical use it is a statutory requirement to be licensed and inspected by the Competent Authority in the UK, the HTA, and to comply with their Codes of Practice. For those involved in assisted reproduction using donor's own or donated gametes and embryos, it is a statutory requirement to be licensed and inspected by the Competent Authority in the UK, the HFEA, and to comply with their Code of Practice.

2.6. A continuing audit of the outcome of tissue and organ transplantation is an essential part of maintaining and improving safety. The reporting of adverse outcomes of such treatment is an important component of their strategy and is discussed in more detail in Section 11.

3. Referral for donation

Deceased donors

Controlled and uncontrolled organ donors after cardiac death (DCD)

3.1. In recent years, there has been an increase in the number of organs donated for transplantation from patients who have been certified dead in the conventional manner by cessation of a heartbeat. These patients are often referred to as donors after cardiac death (DCD), or previously as non-heartbeating donors. Where a patient dies unexpectedly with no time to make efforts to prepare for organ retrieval (this is termed "an uncontrolled DCD") there may be very tight time limits for gathering necessary information. This is primarily applicable to patients presenting in the A&E department. There are also circumstances where for clinical reasons death is inevitable and this outcome can be predicted (this is termed "a controlled DCD"), for example when there has been a separate and clear decision to withdraw curative treatment on the grounds of futility of treatment for the patient. In this situation, there may be more time for information gathering before circulatory arrest and organ retrieval.

3.2. In all cases of potential organ and tissue donation, trained staff should determine whether the deceased person had given consent for organ or tissue donation by checking with the NHS Organ Donor Register (ODR) or any other source, such as a will. If consent (authorisation in Scotland) is established, the deceased person's relatives or those close to them should be informed of the wishes of the deceased. The possibility of organ or tissue donation should be discussed, making them aware of the primacy that should be given to the wishes of the deceased, and ensuring that practice adheres to the Human Tissue Act 2004, together with the HTA Codes of Practice on consent. Where the wishes of the deceased have not been recorded, consent for donation may be given by a person in a qualifying relationship.

3.3. A hierarchy for obtaining consent and the procedures to be undertaken to ascertain whether a living or deceased donor wishes to donate are contained within the HTA Codes of Practice (Codes 1, 2 and 6) which apply to England, Wales and Northern Ireland, and in the Human Tissue Act (Scotland) 2006.

Organ donors donating after brain death (DBD)

3.4. All clinicians responsible for the care of patients who, following brain stem testing, have been declared dead while on respiratory and circulatory support should consider the potential of that patient for donating organs and tissues. All patients who are potentially brain stem dead should be tested and referred to the donor transplant co-ordinator – now renamed as Specialist Nurses in Organ Donation (Specialist Nurse-ODs) – regardless of any potential or actual infection risk that may have been identified. Not all infections present in donors are reasons for donor exclusion, and the balance of risk and benefit may favour the use of donations carrying an infection risk in some situations, whilst in others the same donations would not be considered fit for purpose.

Deceased tissue-only donors

3.5. In circumstances where circulatory arrest has occurred, tissues that are not rapidly degraded (such as corneas, bone, heart valves, tendons and skin) may still be suitable for transplantation even though the donor is not suitable for the donation of organs. All categories of deceased donors (DBD, controlled and un-controlled DCD, including donors after organ recovery) should also be considered as potential tissue donors. In the case of potential tissue donors, accident and emergency departments and many non-clinical

professional groups (including the police) may refer potential donors and their families to tissue establishments or Specialist Nurse-ODs.

3.6. The donor's family and/or most relevant life partner should be interviewed, and relevant health professionals contacted, such as the donor's GP. Standard questionnaires should be used to seek relevant information and should be kept as part of the donor record in keeping with regulatory requirements. Wherever possible any post mortem findings will need to be available to ensure that an appropriate risk assessment is complete and that all information pertaining to the cause of death is taken into account.

Risk assessment for deceased organ donors

3.7. Current microbiological results on the donor should be available from the patient's clinician and must be included in the comprehensive patient assessment process conducted by the Specialist Nurse-OD. In the unusual situation where clinical circumstances dictate the need to consider such an action, the risk arising from the use of materials from potentially infected, or known-to-be-infected donors should be discussed with a consultant microbiologist/virologist. Advice from a specialist centre may be required for defining the balance between risk and benefit. Such discussion is normally between the receiving organ transplant unit and the relevant consultant microbiologist/virologist, in the context of the information gathered by the Specialist Nurse-OD which must include the relevant microbiological findings. Sections 8 and 9 summarise the recommendations of this guidance for microbiological testing and risk assessment.

Living donors

3.8. Circumstances for living donations are different. Some people want to donate an organ to a relative or other person they are close to. The potential pool of living donors has recently been extended to include paired donation, paired pool donation and non-directed altruistic donation. Others may agree to donate surplus tissue (for example, heart valves from the diseased heart after heart transplantation, bone following hip-replacement surgery, or umbilical cells to a cord blood bank). The information needed to assess any risk should be gathered from the potential donor or, in the case of child donors too young to understand the issues, from the adult with parental responsibility for that child as specified by the Human Tissue Act 2004 and the current HTA Code of Practice on consent.

3.9. Donors of bone marrow and peripheral blood stem cells lacking the capacity or competence to consent (this may include adults and children), must be assessed by an accredited, independent assessor (IA) and the results of this assessment be submitted to the HTA for approval. The HTA trains IAs to assess certain types of living organ transplantation in the UK. The types of transplantation include paired, pooled and non-directed donations and the use of sibling paediatric donors for stem cell transplants. The IAs act as both a representative of the HTA and as an advocate of the donor.

3.10. Autologous donation is a special example of living donations where tissue previously taken from an individual is subsequently transplanted to meet that same individual's clinical needs. This removes issues relating to immune-rejection and infection risks from third party donors, but where processing and storage are necessary the procedure may still carry risks of microbiological contamination from the environment. Furthermore, microbiological screening of the donor prior to the procedure is a requirement of the Human Tissue (Quality and Safety for Human Application) Regulations 2007, especially where tissues may require processing and storage in communal facilities. The HTA has a statutory requirement that all samples awaiting results are quarantined regardless of ultimate destination. An autologous donation from an infected donor must be stored securely in a way that does not pose an infection risk to other donations stored in the same facility. Segregation is advisable.

Donors of reproductive cells, embryos and embryonic stem cells

3.11. The various uses of reproductive cells are not equivalent to organ or tissue transplantation. Their use in the human body carries a risk of infection transmission and other potential adverse effects not only to recipients, but also to any child that might result from fertility procedures. The specific circumstances in which gametes, embryos and stem cells derived from embryos might be used require special consideration.

3.12. Guidance on the assessment of living donors of reproductive cells (sperm, eggs and embryos) is outlined in Guidance note 11 (Donor recruitment, assessment and screening) of the HFEA Code of Practice. Special legislation applies for sperm, eggs and embryos where specific written consent needs to be in place from the donor for storage and subsequent use. Post mortem use is permitted but only with the donor's written consent. Specific consent must also be obtained as to whether the donor of sperm wishes to be registered as the father of the resulting child, even after death. All sperm, eggs and embryos must be traceable to the donor. Traceability data must be kept for a minimum of thirty years and in a form that allows adequate investigation should a problem be identified after the sperm, eggs or embryos have been used.

Donation of gametes

3.13. Donors of gametes are expected to be selected on the basis of their age, health and medical history, provided by a questionnaire and through a personal interview performed by a qualified and trained healthcare professional. This assessment must include relevant factors that may assist in identifying and screening out persons whose donations could present a health risk to the recipient, or any child that might result, such as the possibility of transmitting genetic or infectious diseases, including sexually transmitted infections. For partner donation, requirements for infection testing are less stringent since the couple will have been cohabiting and thus exposed to infection naturally. Tests are concentrated on prevention of infection to offspring, or contamination of others during processing or storage.

Donation of embryos

3.14. Infertile couples seeking IVF procedures (partner donation – see 3.18b) for treatment of infertility may be content to donate embryos surplus to their clinical requirements for the purposes of stem cell derivation or for use in the treatment of others.

3.15. In contrast to sperm donors and other live tissue/organ donors, donation of embryos by couples undergoing IVF is incidental to the main therapeutic process, and it may be more difficult to obtain reliable sexual history information within the context of a fertility interview, as such information might have prejudicial effects on the couple's relationship. This makes the veracity of this information for the purpose of infection risk assessment, even if obtained confidentially in individual interviews, open to question. However, if embryos are to be donated for clinical use there must be a reliable clinical history. The screening and assessment requirements in the Human Fertilisation & Embryology Act (as amended 2008) and the HFEA's Code of Practice apply equally to the people who provided the sperm and egg used to create an embryo, which is subsequently donated, as to gamete donors. There is no lower standard for embryos. Therefore assessment interviews are, or should be, conducted individually to ensure, as far as possible, the veracity of the information obtained.

3.16. The requirements for hESC procurement, derivation and culture are complex:

- Derivation of stem cell lines from human embryos *in vitro* falls under the Human Fertilisation and Embryology Act 1990 (as amended in 2008) because it involves the

use of live human embryos, and is regulated by the HFEA, which publishes guidance through its Code of Practice;

- Responsibility for adhering to the Act and the Code of Practice rests with the Person Responsible of the assisted conception unit, as named on the HFEA licences for treatment, storage and/or embryo research;

- For research purposes, embryos may not be kept *in vitro* beyond 14 days (or the stage of presumptive formation of the primitive streak, if earlier). For stem cell derivation they are disaggregated from their usual morphological conformation before this point. Once derived, embryonic stem cells are outside the scope of the HFEA;

- Production of stem cell lines that are intended for clinical purposes and have been derived from human embryos fall under the Human Tissue (Quality and Safety for Human Application) Regulations 2007 and HTA licensing arrangements, until their development reaches a stage where they have a definite therapeutic application and will be considered an ATMP. At this stage, they fall under the jurisdiction of the Medicines and Healthcare products Regulatory Agency (MHRA);

- In view of the potential for the wide-spread use of, and the exposure of multiple recipients to, ATMPs derived from hESCs and iPS cells, and the extensive *in-vitro* processing required, a more cautious approach is likely to mandate stringent microbiological screening for a wide range of agents. This lies outside the scope of this guidance;

- Further guidance relating to the regulatory requirements for conducting human stem cell research can be obtained via the UK Stem Cell Tool Kit. The establishment undertaking this development will require an HTA licence under the responsibility of the HTA Designated Individual.

3.17. Embryonic stem cells uniquely present an unusual opportunity for multiple testing of expanded banked cellular material not afforded to one-off use of organs and most tissues. Although tests such as NAT may not yet have been validated for use on these tissues, in time this may allow increased confidence for such *in vitro* safety tests, and reduce the need for historical reliance on initial testing of donor samples.

Risk assessment and mitigation

3.18. We consider five different applications where recipients of “reproductive cells”, including all tissues and cells for the purpose of assisted reproduction, might be at risk of acquiring an infection and indicate appropriate means to reduce or prevent transmission of infectious agents.

a. Partner donation with direct use (i.e. gametes (sperm and eggs) used with no processing or storage, in an attempt to achieve pregnancy in a partner)

The EUTCD (2006/17/EC) gives special consideration to the direct use of gametes between partners that have an intimate physical relationship where the gametes are used directly without any processing or storage. In such partner donation it is acknowledged that less stringent biological testing may be needed, compared with donation from third parties (Annex III of EUTCD 2006/17/EC). However, in order to minimize the risk of cross contamination, equivalent biological testing is required when the donated cells will be processed, cultured or stored. This requirement was brought into UK law through the Human Fertilisation and Embryology (Quality and Safety) Regulations 2007, which revised the Human Fertilisation and Embryology

Act 1990 to reflect the provisions of the EUTCD. Thus testing is not required for intracervical or intravaginal insemination, but would be required for intrauterine insemination (IUI) and gamete intrafallopian transfer (GIFT) – see (b) below. In the case of sperm processed for intrauterine insemination and not to be stored, if the tissue establishment can demonstrate that the risk of cross contamination and staff exposure has been addressed through the use of validated processes, biological testing may not be required.

b. Partner donation with *in vitro* manipulation (i.e. gametes (sperm and eggs) are processed in the laboratory, or stored, or used for IVF or intracytoplasmic sperm injection (ICSI) or GIFT

In this case full testing of both partners is mandatory according to Annex III of EUTCD 2006/17/EC (as implemented by the Human Fertilisation and Embryology Act 1990) and the HFEA Code of Practice. A special circumstance may arise where assisted reproduction is used to avoid transmission of HIV, hepatitis C or CMV from the semen of an infected individual. In these cases 'sperm-washing' can be undertaken as a risk reduction strategy, but it is appropriate practice that the sample for insemination is tested after processing to confirm it is free of detectable viral RNA.

c. Donation of gametes and embryos for use by third party

Sperm, eggs or embryos may be donated for use by a third party. In practice these are generally only used after processing and cryopreservation. However, it is only relatively recently that human eggs can be cryopreserved efficiently, such as by vitrification, and in some circumstances eggs are donated to a third party immediately after retrieval as part of egg-donation or egg-sharing protocols. It is not yet mandatory for these eggs to be quarantined using cryopreservation before use. As with other tissues and organs, risk can be reduced, both in terms of the recipient and the welfare of any resulting child, by careful donor selection, and NAT testing of each partner involved. Screening for sexually transmissible infections, chlamydia and gonorrhoea, in addition to syphilis testing should also be undertaken prior to non-partner donation.

d. Embryonic stem cells for therapy created from gametes or embryos that have not been cryopreserved

Embryonic stem cells created from gametes and embryos (classified as ATMPs) are considered potentially useful in regenerative medicine. Such cells have been isolated from human blastocysts, or individual blastomeres from embryos surplus to individual therapeutic needs as part of assisted conception procedures. Although in the future it may be possible that these cells could be suitable for own/partner use, generally they would be donated for use by third parties. Hence it is appropriate that like other tissues and organs for transplantation, appropriate history-taking and microbiological testing of both partners is undertaken. In addition, traceability of procurement and processing are needed for later scale-up and use as a therapeutic product.

e. Embryonic stem cells for therapy created from cryopreserved embryos

Embryonic stem cells created from cryopreserved embryos (classified as ATMPs) are considered potentially useful in regenerative medicine. Under UK law, embryos may normally be stored by the couple for up to 10 years, 55 years in exceptional circumstances (Human Fertilisation and Embryology Act 1990, as amended 2008).

Couples who have completed their family may consider donating their stored embryos which they no longer wish to use for third party use or for research which may include derivation of stem cell lines for therapeutic use. In such cases appropriate safeguards in terms of history, microbiological testing of the couple and clear traceability of procurement, processing and storage are needed. Where an embryo has been used to derive stem cell lines and it has not been possible to retrieve donor samples for testing, extensive *in vitro* testing of the ATMP may be used to identify any residual risk.

Table 2 – Type of Donor

Type of donor		Circumstances surrounding the donation	Example
Deceased	DBD (Heartbeating)	Retrieval from donor certified as dead by brain stem testing while on respiratory and circulatory support.	All organs and tissues
	DCD (Non-heartbeating)	Retrieval of **organs** usually within one hour but not beyond 4 hours of circulatory arrest.	Kidney Liver Lung Pancreas and islet cells Eye/cornea*
		Donations of **tissues** up to 48 hours after death.	Heart Valves Bone Tendons Skin Cartilage
Living Allogeneic	Directed	A donation from a living relative or someone emotionally related. Related HPC donors e.g. a sibling or parent.	Kidneys Liver, Lung (occasionally) Limbal stem cells HPC HPC-marrow HPC-apheresis HPC-cord blood
	Voluntary unrelated donation of organ or tissues to an unknown individual	Standard altruistic donation of organs and tissues. Large registries are now available nationally and internationally in order to select volunteer unrelated HPC for transplantation.	Kidneys Bone Reproductive cells HPC-marrow HPC-apheresis HPC-cord blood hESCs iPS

Type of donor		Circumstances surrounding the donation	Example
Autologous	Tissues and cells	Procedures involving retrieval of tissues and cells for later use in the donor.	Skin Bone Keratinocytes Limbal stem cells HPC-marrow HPC-apheresis Cartilage Tendon Reproductive cells

*Retrieved as soon after death as possible and within 24 hours maximum

4. Donor assessment and accountability

Donor assessment

4.1. Once a consented donor has been identified there are two principal components to assessing the suitability of this donor as a source of human materials for clinical use.

4.2. The first component comprises a clinical risk assessment based upon an interview, which addresses the likelihood of a donor having been exposed to a variety of infection risks. This interview is an opportunity to explain the consequences of making a donation, including testing, possible results and the impact of positive results on the contacts of the donor. In the case of deceased donors the most relevant life partner or close relative should be interviewed to ascertain the medical, behavioural and travel history. Additional information may be available from the referring clinician, the primary healthcare practitioner, the donor's GP, post-mortem and/or examination at the time of tissue procurement or organ retrieval. The information required for assessing the infection risk from donors is set out in the NHS Blood and Transplant Patient Assessment Form (PA1) – current version is August 2009 – or equivalent and accompanying rationale. These data do not necessarily exclude donation but are required to inform the final balance of risk and benefit analysis prior to transplantation.

4.3. A physical examination of the deceased potential donor should be undertaken at the time of organ and tissue retrieval. This may indicate extra risks of infection. For example, needle marks on the potential donor could indicate possible risk behaviour and should be taken into account when assessing the donor suitability. In the case of potential organ or tissue donation, a physical assessment body map is completed by the Specialist Nurse-OD or the Tissue Services retrieval team respectively, to annotate any potential signs of infection risk.

4.4. Detailed information is also required on the following:

- Any treatment received before donation (including the choice, duration and dose of antimicrobial and other drug therapy);
- Any history of receipt of blood, blood components, blood products, tissue or organ graft;
- Any previous or current immunosuppression (by disease or drugs) as this may affect the interpretation of test results or the donor's suitability. For example, seroconversion may be greatly delayed by host immunosuppression and the serological response attenuated. However, both combined antigen/antibody tests and NAT testing for viral genome would be expected to detect infection efficiently in this situation and remove the concern of potential attenuation of the antibody response;
- Consideration needs to be given to plasma dilution, see paragraphs 5.18 and 5.19 for further details;
- Any travel history outside of the UK. This is to assess the risk of potential transmission of exotic infections, e.g. malaria, West Nile virus and rabies;
- Any history that may have put the donor at risk of transmissible spongiform encephalopathies (TSEs), e.g. exposure to material of CNS origin including pituitary-derived growth hormone and gonadotrophin, brain and spinal surgery, familial history of TSEs or progressive neurological degenerative diseases of unknown aetiology, or notification to an individual that they are at increased risk of vCJD;

- Any history of malignancy, recent infectious disease or exposure to an infectious disease that may affect the safety of donation;

- Any behavioural history that could have put the donor at risk of blood-borne viruses. This will include questions about risk behaviours such as recreational drug use, men who have sex with men (MSM), and risks such as accidental body fluid exposure;

- Results of any recent microbiological tests must be made available and should be reviewed.

4.5. The second component comprises appropriate microbiological testing. Whilst medical and behavioural assessment will be similar for all donors, the actual microbiological assessment will vary for different types of donors. Sections 8 and 9 set out the recommendations for testing and action to be taken on the results. The results of the donor-suitability assessment will inform the balance of risk and benefit in deciding whether a donor is suitable in particular transplant situations.

4.6. The balance of risk and benefit is carried out by the recipient's transplant surgeon, who must be able to assess correctly the risk of a potential donor having an infection, or having been exposed to an infection. The risk benefit analysis will consider different factors depending on the type of donor (see Table 2) and whether organs, tissue or cells were donated. Furthermore this process will take into account whether the transplant is life-preserving (e.g. organs, skin, HPC), life enhancing (e.g. sight saving ophthalmic transplants, bone for improved mobility and pain relief) or life-producing (to aid reproduction, in which case consideration must be given to the well being of the conceptus). It will also consider whether retrieved material must be transplanted immediately or whether material can be stored and/or processed in a laboratory before transplantation.

Accountability – organ donation

4.7. In the case of organ donation, the new EU Directive (2010/53/EU) lays down the requirement for Member States to develop a framework of Competent Authorities responsible for the safety and quality standards of organs donated for human use. At present the ultimate responsibility for use of a donated organ lies with the recipient's transplanting surgeon.

4.8. For organ donation, all the information gathered should be kept in the donor's records and the records of the person receiving the transplant for 30 years after clinical use or expiry. All information carried into the recipient's notes must be anonymised with respect to the identity of the donor to protect against identification of the donor to the recipient. This should not compromise full traceability from donor to recipient.

Accountability – tissue and cell donation

4.9. In the case of donated tissues and cells, the Medical Advisor of the cord blood bank, tissue establishment or bone marrow registry is responsible for making sure the risk of infection is assessed as accurately as possible.

4.10. In the absence of a Medical Advisor, the responsibilities around donor assessment and testing lie with the Designated Individual of the tissue or stem cell laboratory or storage facility, the Assisted Conception Unit or HPC clinical collection facility. These units are collectively referred to as the tissue establishments. There are well defined roles for tissue establishments in national legislature for which the HTA is the Competent Authority. HTA licensed authorities are required to comply with HTA Directions 003/2010, which came into force on 12 November 2010. These Directions consolidate and clarify the standards required

under the Human Tissue (Quality and Safety of Tissues for Human Application) Regulations 2007.

4.11. There is also guidance on tissue and cell donation from several professional groups, national and international (for example from the Foundation for the Accreditation of Cellular Therapy (FACT). Unrelated donor registries should also conform to all relevant national and international requirements and guidance. Traceability and responsibility for reporting adverse events to the Competent Authority lies with the HTA and HFEA licensed establishments and their designated individuals for the licences.

4.12. The requirements for Assisted Conception Units and the use of embryos for stem cell derivation are covered in the HFEA Code of Practice. Guidance relevant to reproductive cells is given in guidance note 11 of the HFEA Code of Practice. Embryos, and tissues derived from them up to 14 days from fertilisation, may only be handled under licence from the HFEA, and on premises licensed by them. Once the embryo is disaggregated, handling of the derived tissues, if intended for human use, falls under the Human Tissue (Quality and Safety for Human Application) Regulations 2007.

4.13. In the case of tissue donations, all of this information should be retained in the donor's record at the tissue establishment. All donations should be coded to allow recipient hospitals to maintain a two-way audit trail between donors and recipients to facilitate traceability. Full traceability from donor to recipient must be retained as per HTA Directions 003/2010 and the necessary anonymisation, to prevent identification of the donor by the recipient, should not compromise this requirement.

5. Collection of material for donor testing

Deceased organ and tissue donors

5.1. Deceased donor blood sampling and tissue retrieval may happen many hours after circulatory arrest. In order to maximise the quality of the materials retrieved for testing, retrieval should only be undertaken by trained staff.

5.2. Where ante-mortem blood samples taken for other purposes exist, these samples (taken up to seven days preceding death) are usually preferable to post-mortem samples. Appropriate systems should be in place to make sure samples can be identified and stored in optimum conditions.

5.3. Where no ante-mortem sample is available, a post mortem sample can be used, provided samples for testing are taken as soon as possible, and within 24 hours of circulatory arrest. The sample should be inspected for haemolysis before testing - only in exceptional circumstances should a visibly haemolysed sample be used for donor testing. The site from which the sample was obtained and the time of sampling should be documented in the donor's file. Preferred sites for taking samples include cardiac or subclavian puncture and femoral vessel puncture. It is essential to avoid sites close to intravenous lines.

Living donors

5.4. A blood sample taken up to 30 days before organ donation is considered to meet the requirements for testing, as long as the donor's risk status has not changed in the time between the sample being taken and the donation.

5.5. For tissues and cells, serological testing of a sample taken on the day of donation or up to 7 days post-donation, and of a subsequent sample taken 6 months later for donors of tissues and cells which may be stored before use, is considered to meet the requirements for testing.

5.6. Negative results on NAT testing for HBV, HCV and HIV of a blood sample taken on the day of donation, or up to 7 days after donation, from a seronegative individual avoids the need to quarantine cryopreserved donations and retest donors after six months.

5.7. HPC-cord donations are usually initially stored un-tested, but under conditions demonstrated to prevent the donation from contaminating the storage facility (see paragraph 6.14 onwards). Where storage has not been validated to contain any potential infection risk, donations should be quarantined separately if cryopreservation precedes microbiological testing. A maternal sample taken from 7 days prior to donation to 7 days post-donation may be used for serology and NAT testing. Donations from infected mothers should be removed from the storage facility as soon as the infection risk is identified.

5.8. In the case of cord blood banks, there should be a written policy for retesting the relevant microbiological markers before issuing a cord blood unit. This should be done by re-sampling the mother at least 180 days after delivery or by performing nucleic acid testing (HIV, HBV and HCV) on the mother's original sample taken at the time of delivery.

Donors under 18 months or breastfed children

5.9. When assessing infection status in a deceased donor less than 18 months of age, or older children who have been breastfed within 12 months of donation, the testing requirements depend on the age and any intervention risk:

- If the death of the neonate falls within 48 hours of birth, a full microbiological screening of the mother is required;
- For death between 48 hours and 28 days of birth, if there has been no identifiable intervention risk, the same microbiological screening on the mother applies. If, however, there are identifiable risks (eg. transfusion) then a full microbiological testing of the mother and nucleic acid testing of the neonate is required;
- From 28 days of age up to 18 months or within 12 months of breast feeding full microbiological screening of the infant and the mother are both required.

5.10. Early in human life an infant is subject to challenge by a number of infections, some of which can be transmitted from the mother both *in utero*, at birth and in the puerperium/early life. Of the agents which are transmissible by transplantation, CMV, HIV and HBV may be transmitted *in utero* and at birth. HIV, CMV and HTLV may be transmitted after birth and by breast feeding. Interventions in the postnatal period, for example HBV active/passive immunisation and replacing breast milk for HIV- and HTLV- infected mothers may reduce the frequency of viral transmission.

Sample handling and preservation

5.11. Effective and accurate testing of donor samples requires high quality samples of sufficient volume to allow primary testing, confirmation and archiving. In all situations ante-mortem blood samples are preferable. Given the advent of nucleic acid testing as a routine, EDTA anti-coagulated whole blood is preferred to clotted blood for NAT testing as the EDTA inhibits many plasma enzymes and stabilises RNA viruses.

5.12. The sample should be transported to the laboratory as soon as possible and marked urgent preferably with prior notice given to laboratory staff. Prolonged transportation or storage should be at 4°C, but not frozen. Blood samples should be separated on receipt in the laboratory; extra centrifugation to clarify serum or plasma may reduce the false reactivity rate of deceased donor samples.

Validating testing

5.13. The principles for determining the infection status of donors of organs, tissues and cells are based on the principles that have been established for screening blood donors. The tests used should be CE marked and meet the same standards of accuracy and timelines as required for the screening of blood donors. It is recommended that tests of similar sensitivity and specificity as those assays considered suitable for use by NHSBT[2] should also be used for organ and tissue donors. Full quality assurance procedures should be in place for all tests in routine use. All blood samples taken for testing must be accurately identified and labelled with records retained to ensure continuing linkage of donor details with the donor sample(s).

5.14. Nucleic acid tests are now available including triple tests for HIV, HBV and HCV genomes on automated platforms. They are now used routinely in blood services and have been validated

[2] List of tests available through the Secretary to the Kit Evaluation Group (KEG) at NHSBT on 0113 820 8731

by blood services and HPA (NIBSC) for use in screening tissue donors including the testing of deceased donor samples. Individual laboratories are encouraged to validate these assays in accordance with their standard operating procedures.

Testing blood from deceased tissue and DCD donors

5.15. As time passes after a donor's heart stops beating it becomes more difficult to test samples taken from that donor as the blood has often deteriorated. Post-mortem blood samples should therefore be collected as soon as possible after the donor's death and within 24 hours following circulatory arrest. Any testing beyond this time will require appropriate validation.

5.16. Tests validated for deceased donor blood samples should be used if available, provided they are of acceptable sensitivity and specificity. Inhibitors to NAT tests in deceased donor samples may generate false negative results but may be detected by the incorporation of appropriate internal controls in the assays.

5.17. The time of death together with the time and location of sampling must be recorded. If available, an ante-mortem sample is always preferable.

Plasma dilution

5.18. When massive blood loss has occurred, all intravenous infusions the donor received in the 48 hours before death or before the taking of a blood sample for microbiological testing (including colloids, crystalloid and blood or blood products including immunoglobulin), should be assessed in order to determine potential donor plasma dilution and the subsequent validity of serological tests.

5.19. It is also necessary to ensure that the sample obtained for the analysis has not been diluted by venesection in close proximity to any intravenous infusion site. If a pre-treatment sample is not available, consideration should be given to the degree of potential dilution of plasma which could have occurred, though in practice the sensitivity of current serological assays is such that significant loss of detection sensitivity is unlikely. NAT testing will have a role in this situation. Organs may potentially be transplanted if this information is not available, on a basis of risk and benefit analysis as determined by the transplanting surgeon.

6. Retrieval of material for donation testing

Sterility of organ donations

6.1. Donor organs are removed under the sterile conditions of a surgical operation and transported cooled and bathed in fluid. On transplantation, the fluid surrounding organs intended for transplant during transportation should be cultured for bacteria by standard methods. If the sample is negative for bacteria, no further action is necessary. If positive an assessment of the pathogenic potential of the species isolated should be made and appropriate antimicrobial cover given if deemed necessary. In the event of a post transplant septic episode in the recipient, the bacteriological test results will support the investigation of the source of infection.

Retrieval of tissues

6.2. Tissues should be retrieved as soon after death as possible, and within 6 hours if the body is not refrigerated. If the body has been refrigerated within six hours of death, retrieval must be completed within 48 hours of death; however, eyes must be retrieved within 24 hours.

6.3. Tissues should be recovered in a suitable facility which must be either a HTA licensed premises or licensed under a third party agreement. They should be recovered using local sterile fields to minimize cross contamination with microbes from other body sites. Where possible, sterile single-use instruments and equipment should be used with a minimal number of appropriately gowned and masked retrieval staff in attendance. Where re-usable instruments have to be used, these should be cleaned, sterilised and fully traceable to allow a record of which specific instruments were used on any given donor.

6.4. Retrieval should preferably precede any post mortem examination of the donor and no other activities (embalming, autopsy or other tissue donor recovery) should occur at the same time in the facility. However, on occasion, and subject to an appropriate risk assessment, tissues outside of the abdominal cavity (e.g. heart, eyes and skin) may be retrieved at, or after, post-mortem. There are currently no guidelines for the environmental monitoring of mortuaries – consideration should be given to their future development.

Microbiological testing of tissue samples for transplantation

6.5. Tissues should be processed and screened for microbial contamination by validated methods, the mandatory requirements of which are outlined in the HTA Directions 003/2010. Representative pre-processing samples (e.g. bone or bone chips, pieces of tissue or swabs of tissues) should be transferred aseptically into appropriate culture media at the time of processing.

6.6. Controlled work areas of tissue processing facilities should be monitored by air, surface contact and glove print sampling to ensure that bacterial counts fall within the grade designation of the facility.

6.7. Samples of the tissue must be taken before and after the tissue is exposed to decontamination agents. Enrichment liquid cultures should be used to maximize the recovery of aerobic and anaerobic bacteria and fungi.

6.8. If pathogenic, highly virulent organisms are recovered (e.g. *Clostridium* spp., *Streptococcus pyogenes*), the tissue should not be used for transplantation unless it is effectively sterilized by a process such as gamma irradiation. Tissues contaminated with bacterial species of low virulence must be decontaminated by a validated process.

6.9. Tissues which cannot be terminally sterilized must be discarded if post decontamination culture tests are positive: an exception is cryopreserved skin allografts which can be transplanted if only non-pathogenic bacteria in low numbers are present.

6.10. Once an individual tissue fails bacteriological testing, other tissues from the same donor should be discarded unless a risk-benefit analysis shows otherwise. For example, discard of contaminated tendons might not necessitate the discard of appropriately bacterially-tested heart valves if they were processed separately.

6.11. The acceptance criteria for specified tissues, and the identification of organisms which are also considered acceptable at the various stages of processing, should be documented in written policies through consultation with a designated microbiologist. Advice should be sought for tissues that give equivocal or inconsistent bacteriological test results.

6.12. Bioburden estimations of marrow-depleted bone are not considered to be of value as the process of removing marrow effectively reduces microbial load. Similarly, estimation of bioburden of skin and amnion is not recommended as the former carries a substantial bioburden and the latter is surgically recovered under aseptic conditions. However, a heavy growth of bacteria from pre-process samples may signify gross contamination and the tissue should not be released unless able to be terminally sterilized by irradiation or other techniques. The potential damage to the integrity of the tissue by the high numbers of bacteria should also be considered before it is used for transplantation.

6.13. A number of tissues, including cryopreserved cardiovascular allografts, amniotic membranes, menisci or osteochondrals, cannot be irradiated. These may be decontaminated with mixtures of antibiotics. The antibiotic solutions used should be validated to be effective against the range of bacterial species normally recovered from such tissues and the tissue bank should develop a list of species exclusion criteria based on an assessment of the clinical risk of serious infection in the recipient. Cardiovascular tissues must also be tested for *Mycobacterium* spp., and fungal contamination using validated techniques.

Storage of retrieved donations by cryopreservation

6.14. Tissues consisting of viable cells for transplantation will often require long-term cryopreservation prior to use. In the past, storage in the fluid phase of liquid nitrogen has afforded the opportunity for microbial contaminants to gain ingress to the stored materials. In one unit, this led to a series of HBV infections in recipients whose bone marrow autografts were stored in a contaminated tank. As a result of this a series of recommendations for cryopreservation were made. These apply to the storage of tissues retrieved for use as allografts by third parties as well as tissues stored for subsequent use as autografts.

6.15. It is appropriate to reduce the contamination risk by routinely storing donations in the vapour rather than the liquid phase of nitrogen, and considerable validation of this has been carried out by NHSBT. Where this is not considered possible, donations should be stored in a primary container into which access by liquid nitrogen is prevented. A secondary container should enclose the primary container, further reducing the likelihood of liquid nitrogen washing material in and out of the primary container. Once validated, such a process can be deemed to isolate an unscreened sample within the storage tank, and complies with the need for quarantine before test results are available. This may be desirable but prove not to be possible for very delicate tissues, such as human embryos and hESCs cryopreserved by vitrification and stored in open pulled straws, although sealed straws and closed systems are now becoming available.

6.16. In view of the recognised potential for contamination of material with adventitious agents, local risk assessments must be used to guide best practice. Contamination in this way may

become a concern for the repeated cryopreservation of derived cell lines. Where it is not possible to store donations in a manner which prevents contamination, it is advisable to have separate storage facilities for each known infectious risk. Storage tanks should be cleaned and decontaminated in the event of thawing. If it is found that an infectious unit has inadvertently been placed in the routine storage facility, a risk assessment should be undertaken to define any potential hazard for recipients of materials who have received material from the tank or may receive material in the future.

6.17. Donors of materials intended for cryopreservation should be screened for microbiological infection at the time of retrieval, or in the case of HPC donation within the preceding 30 days. Quarantine of samples until testing results are available is a requirement of HTA Directives. To preserve the integrity of storage tanks in use only donations known to have come from uninfected donors should be placed in the tank. If the timing of procedures is such that cryopreservation is required before the results of microbiological testing can be made available, the use of a holding tank should be considered in which cryopreservation can be performed before long-term storage. This applies unless the conditions of storage can be expected to prevent the possibility of contamination (as above in paragraph 6.15).

6.18. Where automated platforms are used for cryopreservation, donations identified to come from infected donors should be removed after cryopreservation to a separate long-term storage facility. The geographical separation from the routine storage facility to a secure site for infectious donations which cannot be discarded, for example an autologous bone marrow or a semen donation from a person about to undergo radiotherapy, removes the possibility of a third party being put at infection risk from mislabelling or the use in error of a wrong donation. It also reduces possible contamination of the storage facility.

Requirements for laboratories testing donations

6.19. Microbiological tests for donation and transplantation should be carried out only in accredited laboratories licensed by the HTA or through a third party agreement with a HTA licensed establishment.

6.20. Microbiology laboratories that test serum or plasma samples from organ donors should:

- be UK Accreditation Service (UKAS)/Clinical Pathology Accreditation (UK) Ltd. (CPA) accredited;
- have a Consultant microbiologist/virologist available at all times for the interpretation of results;
- have Biomedical Scientists on call at all times for testing;
- consider having two different assays available of similar sensitivity for parallel testing for each of the mandatory markers where these are commercially available. This enables more rapid determination of the status of samples giving repeat reactive results.

6.21. The tests used should be CE marked and meet the same standards of accuracy and timelines as those used for the screening of blood donors. It is recommended that tests of similar sensitivity and specificity as those assays considered suitable for use by NHSBT[3] should also be used for organ and tissue donors. Combined antigen and antibody assays should be used for HIV screening and also merit consideration for HCV testing. Assay runs

[3] List of tests available through the Secretary to the Kit Evaluation Group (KEG) at NHSBT on 0113 820 8731

for screening donors should include the following NIBSC standards in order to validate the test run:

- Assays for anti-HIV must be able to detect HIV NIBSC 99/750 or equivalent in the donor screening run to be valid;

- Assays for anti-HBV must be able to detect 0.2 IU/ml of hepatitis B surface antigen (HBsAg) in the donor screening run and must be known to be secure in the detection of immune and other HBV escape variants;

- Assays for anti-HCV must be able to detect HCV NIBSC 02/238 or equivalent in the donor screening run to be valid;

- NAT assays for the detection of viral genome should be of similar sensitivity to those currently in use for blood donor screening in the UK. Where these tests are run outside Blood Transfusion laboratories, consideration should be given to adopting the control samples used by the Transfusion laboratories.

6.22. Laboratories should be able to archive for at least 10 years donor blood/plasma samples in a retrievable manner and to keep testing records for a period of 30 years, whether as paper or electronic scans. Appropriate archives of serum and other material should be maintained for microbiological testing. Reasons for this approach include the emergence of new pathogens, the development of new tests and changes in donor selection criteria. Maintaining the potential for retesting will prevent donated and archived tissue and cells being discarded because the risk of infection would not otherwise be able to be reassessed.

7. Transportation and safe handling of tissues and organs

7.1 Conditions of transportation of organs, tissues and cells, including packaging, labelling and time/ temperature, should be compliant with those detailed by the appropriate licensing authority and set out in the Human Tissue (Quality and Safety for Human Application) Regulations 2007 for tissues and cells, and the EU Directive (2010/53/EU) for organs. Unification of labelling style is increasingly important given that organs, tissues and particularly cells are increasingly likely to cross EU member state boundaries and may even be carried globally.

7.2 Guidance for transportation is available from:

- Guidelines for the Blood Transfusion Services in the UK, Chapter 23;
- EU Directive 2006/86/EC Annex VI and VII;
- HTA Code of Practice 8 – Import and export of human bodies, body parts and tissue;
- HTA Directions 003/2010;
- HTM 07-01 – Safe management of healthcare waste – Department of Health;
- HFEA Code of Practice, Section 15: Procuring, processing and transporting gametes and embryos;
- HFEA Directions 0009 – Keeping gametes and embryos in the course of carriage between premises.

8. Microbiological testing of donors and donations

General principles

8.1 To maximise the safety of donations, laboratory testing of the donor for markers of transmissible infection is required in addition to the gathering of clinical and behavioural information. Microbiological testing includes those screening tests which are mandated by statutory requirements in the EUTCD and the new EU Directive on organ transplantation (2010/53/EU) together with those that are considered essential for good clinical practice and some additional tests which may be useful in certain circumstances (Table 3). Confirmatory tests are performed to investigate the specificity of reactivity in the donor sample.

8.2 Appropriate donor samples should be sent to an accredited laboratory for microbiological testing using approved assays. Donor testing must be undertaken at a HTA licensed establishment for testing or under a third party agreement with a HTA licensed establishment for testing.

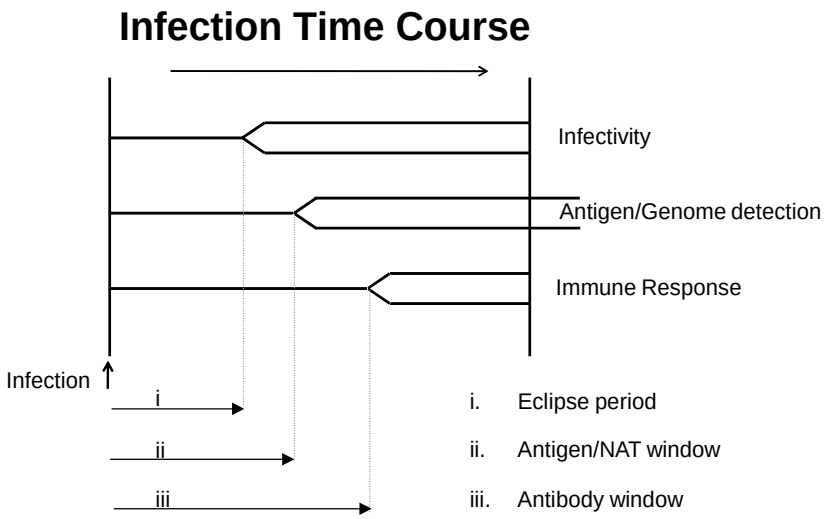
8.3 When assessing a donor for evidence of infection, whole blood anti-coagulated with ethylene diaminetetracetic acid (EDTA) and/or clotted blood samples (yielding plasma or serum respectively) are required. In some situations it may be appropriate to include testing a sample of the donation itself. Samples for testing must be valid, in the case of blood not diluted by intravenous infusions, appropriately labelled and traceable within a quality system.

8.4 Laboratory screening can take the form of serological testing for antibody, for antigen, and molecular testing for the DNA or RNA sequences of infectious agents. The EC Directive currently requires serological testing of donors irrespective of NAT testing (see Table 3). Whilst antibody detection relies on the host response, antigen and molecular assays directly detect components of the infectious agent. Where a donor, or a recipient in the case of testing for serological matching between donor and recipient, has received blood products or components containing plasma immunoglobulins in the preceding six months the interpretation of serological results should take into account the possibility of the individual having acquired antibody passively from the blood product or component.

Time course of an infection

8.5 Following exposure to, and infection by, a microbiological agent there is a period of time during which no microbe can be readily recovered from the host; this is classically called the eclipse period (Figure 1). Donations taken during this period are unlikely to be infectious but in practice this would not be safe and should be avoided.

Figure 1: Diagrammatical representation of the eclipse and window periods



8.6 The time from infection to the onset of detectable infectivity depends upon the method used for detection of infection. This period of infectivity which cannot be detected is colloquially called a “window” and represents the duration of undetectable infectivity. This “window” is shortest for genomic (nucleic acid testing, NAT) and antigen tests, and longest for antibody tests. For practical purposes, the time from infection to first detection of a marker is referred to as the “window period”.

8.7 A donation given in the window period has the potential to cause an infection in the recipient. This applies both to infections which are usually completely cleared, as well as to those giving rise to chronic infections.

8.8 Until the advent of NAT and viral antigen testing (either as a single antigen assay or when incorporated into a combined antibody and assay) there has been considerable reluctance to use donations of any type from a donor whose behaviour may have put them at risk of acquiring a serious transmissible infection. The potential always existed of taking a donation in the window period, and many possible donors were discarded because of perceived infection risks. The potential remains for a donation to transmit an infection acquired in the immediate period before donation and transplanted in the eclipse period. For this reason, questions are still asked of the donor, their clinician and, where appropriate, their family. The use of NAT and/or antigen testing has very greatly reduced the residual risk of infection from recently acquired infections. This should be borne in mind in balancing the benefit of transplantation against the risk of infection.

Changing scene in microbial detection

8.9 Screening tests for detecting infections have improved over recent years with a move from single antibody modality to combination antigen and antibody tests. The co-existence of immunosuppression in a potential donor, either through disease or iatrogenic treatment (e.g. high steroid dosage) should be borne in mind when using an antibody-only test since immunosuppression may delay and attenuate the host serological response. Assays which directly detect the virus are not affected adversely by immunosuppression and thus antigen testing (HBsAg and HCV Ag) and genomic testing (HBV, HCV and HIV NAT) are appropriate in this situation.

8.10 However when using antibody to determine serological status for CMV or EBV matching, the potential for attenuation of the antibody response should be considered. Commercial tests detecting both antigen and antibody ("combo" tests) are now available for HIV and HCV. There is an increasing move to using NAT for detection of microbial genomes. NAT testing, including tests for HBV, HCV and HIV on automated platforms, is increasingly available in diagnostic and routine in blood service laboratories. A test for HCV antigen is now available as a single marker.

8.11 The arrival of fully automated platforms for triple viral nucleic acid testing by at least two manufacturers opens the possibility of 24-hour access to HBV, HCV and HIV NAT testing on demand. These developments have in effect obviated the need for quarantine periods for donations from living donors prior to release of tissue donations. This process was implemented to allow the identification of seronegative but infected donors before release of tissues by detecting a seroconversion at a later sampling time, usually 6 months after the donation. It is now recognised that a NAT test negative for HBV, HCV and HIV at the time of donation from a seronegative individual removes the need for retesting and therefore the requirement for quarantining (EU Directive 2006/86/EC). We note however that the British Fertility Society guidelines recommend adherence to the quarantine protocol for all reproductive cells. Whilst it is recognised that laboratories providing microbiological donor testing outside of UK Blood Services testing centres may not presently have access to NAT testing, the introduction of NAT testing is considered as aspirational good practice.

8.12 The increasing ability to derive clinically relevant cells and tissues exemplified by the *in-vitro* expansion of cell lines and generation of stem cell products which are ATMPs demands tailored microbial detection. This is a rapidly evolving field and the inadvertent coincidental expansion of infectious agents in culture should be considered. The requirements for pre-release testing of such cell lines are complex, and likely to require validated multiplex NAT assays given the wide range of possible microbiological contaminants. They have yet to be decided upon and currently fall outside the scope of this document. However, all source donors of such cells are currently required to undergo testing at the time of donation according to the Human Fertilisation and Embryology Act 1990 (as amended 2008). We note that the extended time period available for testing of these expanded lines should allow comprehensive post-production pre-release testing and that this might have a bearing on the need for pre-donation testing.

8.13 Some human materials may exhibit an innate inability to transmit infection, either because of the nature of the material, or through partitioning of infection away from the product, or through pathogen inactivation (which may be deliberate), or the result of processing before use. For example, the cornea, being avascular, is considered unlikely to transmit Human T-cell Leukaemia Virus (HTLV) or malaria. Where a material destined for human use has been shown not to transmit an infection, or when its processing has demonstrated removal of infection, or where there is a deliberate and validated pathogen inactivation step, or a combination of more than one of these parameters, a risk analysis may allow modification of the testing requirements at the time of donation. This may be particularly relevant to the generation of stem cell lines where prolonged culture, often with antibiotics, may prevent the transmission of infections (e.g. *T. pallidum*). Where a risk analysis identifies that the risks of transmission have been mitigated as described above, it may be appropriate to consider removing the necessity for donor screening.

8.14 The potential for transmission of the aetiological agent of TSE has generated a need for tests to identify donors infected by the causative agent of human TSE diseases. Blood tests of sufficient sensitivity and specificity for donor screening are unlikely to become available in the near future, however in some situations donor tissue may be the best material to test and this option is now being studied.

Table 3 – Screening of candidate organ, tissue and cell donors

	Available tests		Organs*	Tissues**	Haemopoietic progenitor cells (HPC) and therapeutic cells (TC)**	Reproductive cells***	Human embryonic stem cells
Infection	**Serological**	**NAT**					
HIV1/2	Anti-HIV1/2	HIV RNA	✓	✓	✓	✓	✓
HBV	HBsAg	HBV DNA	✓	✓	✓	✓	✓
	Anti-HBc (anti-HBs)	n/a	**a**	✓	✓	✓	✓
HCV	Anti-HCV	HCV RNA	✓	✓	✓	✓	✓
HTLV1/2	Anti-HTLV1/2	n/a	✓	✓	✓	✓	**f**
Syphilis	Anti-*T. pallidum*	n/a	✓	✓	✓	**e**	✓
T. gondii	Anti-*T. gondii* IgG/M	n/a	**b**	**.**	**c**	**.**	**.**
CMV	Anti-CMV	CMV DNA	**c**	**.**	**c, d**	**c**	**.**
EBV	Anti-EBV	n/a	**c**	**.**	**c**	**.**	**f**
C. trachomatis	n/a	*Chlamydia* DNA	**.**	**.**	**.**	✓	**.**
N. gonorrhoea	n/a	*N. gonorrhoea* DNA	**.**	**.**	**.**	✓	**.**

✓ = Mandatory Tests; n/a = not applicable; **.** = not required

***** NAT tests for HIV, HBV and HCV are not mandatory for organ transplantation, but their use represents good clinical practice. Turnaround time will not always permit provision of NAT results prior to organ transplantation, but they should still be performed to ensure the rapid identification of the recipients of potentially infectious organs. If NAT tests are either not done, or the results are not available prior to organ donation, combined antigen and antibody assays (rather than antibody testing alone) are required for HIV, and should be considered for HCV.

** NAT testing is not mandatory for deceased donors of tissues, nor for living donors of tissue and HPC, but it replaces the need for quarantine and the follow-up serological screening. Combined antigen & antibody assays rather than antibody testing alone are required for HIV when NAT results are not available prior to transplantation and should be considered for HCV.

*** Partner donation with direct use does not require microbiological testing.

a Anti-HBc screening is indicated for liver and for tissues but not for other organ donations. As other organs or tissues may be taken from the same donor, in practice the results of this test will often be available. Donors whose serum contains anti-HBc in the absence of HBsAg should be tested for anti-HBs to confirm immunity to HBV infection. Consideration should be given to confirming the specificity of sera which exhibit anti-HBc reactivity in the absence of other markers.

b Donations containing cardiac or skeletal muscle as major component which may contain tissue cysts.

c IgG tests facilitate matching of donor/recipient serological status and risk management in recipient.

d CMV NAT is performed to exclude CMV infection in cord blood donations.

e Syphilis testing of partners is not mandatory under the EUTCD but is routinely a part of antenatal screening; earlier detection of infection would allow treatment and prevention of long term sequelae.

f Good clinical practice

9. Interpreting donor test results

Terminology

Table 4 – Terminology used in the conduct of serological testing

Term	Explanation
Negative	A sample whose reactivity when first tested falls inside the cut-off as defined by the manufacturers' instructions
Initial reactive (IR)	Any sample whose reactivity when first tested falls outside the cut-off as defined by the manufacturers' instructions.
Repeat reactive (RR)	Any sample reactive on two or more occasions (sequential or duplicate) in the same screening test.
Parallel testing	When initial serological testing for a marker is conducted on more than one manufacturer's assay. This procedure, together with testing in duplicate and pre-test manipulation of the sample (clarification and centrifugation), may expedite interpretation of any reactivity detected. Care has to be taken to use assays of similar modality (i.e. antibody or combined or antigen) and sensitivity in parallel testing.
Alternative assay testing	When a test of similar modality and sensitivity is used sequentially rather than in parallel to investigate a sample which is IR or RR in a first screening assay.
Concordant RR	A sample which is RR in two or more serological assays of similar sensitivity. This is likely to indicate potential infectivity.
Discordant RR	A sample giving RR results in one assay but un-reactive in a second assay of similar sensitivity. This is likely to arise following both parallel and alternative assay testing and is unlikely to indicate potential infectivity. It will only apply to those markers where more than one appropriate assay is available for use.
Confirmatory testing	Further testing of a repeat reactive sample using a number of different alternative assays usually in a reference rather than routine laboratory in order to define whether the reaction is specific and indicative of potential infectivity.
Positive	A sample whose reactivity in confirmatory testing meets pre-defined criteria. This may indicate current or past infection depending on the antibody and microbe concerned.

9.1 When an initial serological screening test is reactive (IR), and if it has not been conducted in duplicate at the outset, a repeat serological test in duplicate using the same test system

should be carried out on the same sample before the results are released. If one or more of the repeat tests are reactive the sample should be considered to be repeat reactive (RR). An alternative serological test of equal or greater sensitivity should also be carried out in duplicate, if parallel testing was not undertaken at the outset. The result of the alternative assay testing may inform on the likelihood of the repeat reactivity being a marker for infection.

Table 5 – Terminology used in the conduct of NAT testing

Term	Explanation
Negative	Any sample which when first tested does not signal for the presence of viral genome above the cut-off defined by the manufacturers' instructions.
Initial reactive (IR)	Any sample which when first tested signals for the presence of viral genome above the cut-off defined by the manufacturers' instructions.
Positive (RR)	A sample which signals for viral genome following re-extraction and testing again in the original assay or second assay of similar sensitivity.
Resolved positive (confirmed infection)	A sample which signals for one or more viral genomes in specific assays and leads to the identification of one or more specific infections.

9.2 Commercial NAT assays are of triplex format and detect HBV, HCV and HIV genomes. A sample initially reactive (IR) in NAT may contain one or more of these viral species and will need resolution to specific viruses in a reference laboratory. An IR NAT sample should be retested as soon as possible before referral to a reference laboratory. If it is no longer reactive the donation may be released for use.

Interpretation of repeat reactive and positive test results

9.3 Any repeat reactive serological or NAT test result for HIV, HBV, HCV, or HTLV (serology only) infection, as a rule, normally excludes the use of the donated material. Exceptions may be made however to avoid excluding a donated organ or cells for a life-preserving transplant as discussed in Section 10.

9.4 Where organs or cells from a donor have been sent to other banks or centres, these banks or centres must be told about repeat reactive results. This is to prevent unsuitable organs or cells being transplanted as it often takes a considerable time to get definitive results from confirmatory testing. For tissues with a long shelf-life, no material should be released until all confirmatory testing for a mandatory marker is complete and shown to be negative.

9.5 A positive serology sample is one whose reactivity in confirmatory testing meets predefined criteria which are judged to indicate the presence of the infection for which it is being tested. A positive result will usually indicate current infection but in the case of certain microbial agents may indicate past infection.

9.6 A positive NAT sample is one which signals for the presence of viral genome after re-extraction and testing of the new extract. This indicates infectivity.

9.7 A positive result should be notified urgently to the source bank, Specialist Nurse-OD or supplier of the organ, tissue or cells so that clinicians in all centres that have received

material from the same donor can be informed and take appropriate action. In the case of tissue and cell donors, the results should be available before the tissue is issued. There is a requirement, at local level where the donor was recruited, that protocols are in place for contacting and referring the living donor for further investigation and treatment as appropriate. In the case of a deceased donor, the medical team who provided clinical care at the time of death, or if death occurred outside a health care facility the Specialist Nurse-OD or tissue establishment intending to retrieve the donations, should ensure that those close contacts of the deceased donor for whom results have implications are appropriately informed. There is a need to ensure at a local level that appropriate counselling of affected persons can take place, this is considered a duty of care to the donor and /or donor's family.

Discordant results

9.8 Multiple donor specimens, collected at different time points, are regularly tested for microbiological markers in multiple centres using multiple tests by the time the decision on the donor suitability has to be made. If the results differ, the matter must be resolved in discussion with the consultant microbiologists/virologists concerned, with a final decision being taken by the transplanting surgeon or the medical director of the tissue bank.

9.9 While it may be considered unduly cautious to reject donations on a divergent positive or reactive result, transposition of samples and erroneous reporting are always possible, and such rejection is the safer option. The microbiological significance of a repeat reactive result may become clearer through parallel testing which may have been conducted at the outset or through alternative assay testing. A blood sample reactive in duplicate in one test but unreactive in duplicate in another test of similar or greater sensitivity may be unlikely to represent evidence of infection. If joint consultant opinion indicates the divergent positive reaction to be invalid or the discordant reaction to not indicate infection, the donation can be released.

9.10 We strongly recommend that laboratories undertaking donor screening have established and validated standard operating procedures (SOP) for the investigation and reporting of serological and NAT/antigen testing on potential donors. In particular, where parallel or alternative assay testing reveals discordant results on a single sample, justification for and decision to derogate from exclusion of donation must be clearly explained within the SOPs.

Detailed interpretation of test results by infection

Human immunodeficiency virus (HIV)

9.11 Screening for HIV infection should include a combined HIV antigen/antibody assay, and nucleic acid tests (NAT) for HIV RNA;

9.12 Samples giving repeat reactivity in antibody or combined antigen/antibody assays should undergo confirmatory testing as soon as possible;

9.13 The detection of confirmed anti-HIV 1/2 and/or HIV RNA indicates infection.

Table 6 – The interpretation of a repeatably-reactive serological and/or positive NAT result in an ALLOGRAFT donor – HIV

Test result(s) suggesting possible donor HIV infection	Organs	Tissues	HPC and TC	Reproductive cells	Human embryonic stem cells
HIV 1/2 antibody/ antigen	Contraindication to donation*	Contraindication to donation	Contraindication to donation	Contraindication to donation**	Contraindication to donation
HIV RNA NAT* **	Contraindication to donation*	Contraindication to donation	Contraindication to donation	Contraindication to donation**	Contraindication to donation

***** In exceptional circumstances, a life-preserving donation from an infected donor may be released for clinical use in a recipient who also is infected with HIV in accordance with Section 10. In exceptional circumstances a life-preserving donation from a donor whose serum is repeatably reactive for anti-HIV may be released for clinical use providing the antibody reactivity is shown to be non-specific in confirmatory testing and HIV 1 RNA is undetectable. Consider seeking expert advice concerning HIV prophylaxis and management in the recipient and close contacts.

****** Partner donation of washed sperm for IUI and IVF may be considered in exceptional circumstances.

*** HIV RNA commercial assays differ in their ability to detect viral types other than HIV 1. Since acute HIV 2 and HIV O infections are currently exceptionally rare in the UK, these guidelines do not differentiate between HIV types and refer only to HIV RNA.

9.14 Screening for HBV infection includes testing for HBsAg, anti-HBc and NAT tests for HBV DNA. Samples giving repeat reactivity for HBsAg should undergo confirmatory testing by neutralisation as soon as possible. The detection of confirmed HBsAg and/or HBV DNA indicates current infection;

9.15 Hepatitis B has been contracted from contaminated liquid nitrogen tanks. If cells, gametes or tissues requiring long term cryopreservation from an unscreened donor or an HBV-infected donor are to be stored or processed, see paragraph 6.14 onwards on storage. A donor whose serum contains anti-HBc alone is unlikely to contain HBV DNA at a level which could cause contamination of the storage facility (see the need for risk assessment in paragraph 6.16);

9.16 NOTE: The availability of active and passive immunisation and effective anti-viral therapy allows consideration of departure from these recommendations under circumstances of clinical need and with expert advice.

Table 7 – The interpretation of a repeatably-reactive serological and/or positive NAT result in an ALLOGRAFT donor – HBV

Test result(s) suggesting possible donor HBV infection	Organs	Tissues	HPC and TC	Reproductive cells	Human embryonic stem cells
HBsAg	Contraindication to donation*	Contraindication to donation	Contraindication to donation	Contraindication to donation	Contraindication to donation*****
HBV DNA NAT	Contraindication to donation*	Contraindication to donation	Contraindication to donation	Contraindication to donation	Contraindication to donation*****
Anti-HBc alone and anti-HBs < 100IU/L	Donation permitted**	Contraindication to donation	Permissible for life-preserving transplant	Contraindication to donation	Contraindication to donation***,****
Anti-HBc alone and anti-HBs ≥ 100IU/L	Donation permitted***	Donation permitted	Donation permitted	Donation permitted	Donation permitted

* In exceptional circumstances, a life-preserving donation from an infected donor may be released for clinical use in a recipient who also is either infected with or immune to HBV in accordance with Section 10. Consider recipient infection status in risk assessment and seek expert advice concerning HBV prophylaxis and management in recipient and close contacts.

** Detection of anti-HBc in the absence of HBsAg indicates past hepatitis B virus infection, however donations from a proportion of individuals whose sera contain anti-HBc in the absence of anti-HBs may still be infectious. Although this is unlikely the Tissue Directives require testing tissue donors for anti-HBc. Detection of anti-HBc with or without anti-HBs is a relative contraindication for liver donation. The potential for hepatitis B transmission warrants consideration of appropriate prophylaxis of recipients.

*** If anti-HBs in excess of 100 IU/L is present together with anti-HBc, donations are unlikely to be infectious and donation is permitted with the potential exception of livers (see above). In practice the results of HBV DNA NAT may be available prior to tissue or cell donation. Absence of detectable HBV DNA may also indicate suitability for donation though this does not exclude intra-hepatic sequestration of HBV.

Hepatitis C Virus (HCV)

9.17 Screening for HCV infection employs either an antibody-only assay or a combined HCV antigen/antibody assay and molecular tests for HCV RNA;

9.18 Samples giving repeat reactivity in the antibody or the combined antigen/antibody assays should undergo confirmatory testing as soon as possible. The detection of confirmed anti-HCV indicates past or current infection. RNA detection indicates current infection. Confirmed anti-HCV in the absence of detectable HCV RNA does not exclude use of a life-preserving organ donation in cases of severe clinical need.

Table 8 – The interpretation of a repeatably-reactive serological and/or positive NAT result in an ALLOGRAFT donor – HCV

Test result(s) suggesting possible donor HCV infection	Organs	Tissues	HPC and TC	Reproductive cells	Human embryonic stem cells
HCV antibody/ antigen	Contraindication to donation*,**	Contraindication to donation*	Contraindication to donation	Contraindication to donation***	Contraindication to donation**
HCV RNA NAT	Contraindication to donation*,**	Contraindication to donation*	Contraindication to donation	Contraindication to donation***	Contraindication to donation**

* The immunosuppression associated with organ transplantation significantly increases the risk of disease by accelerating presentation of HCV-related illness. The use of donations from an HCV-infected donor in a recipient who will require immunosuppression should be avoided.

** In exceptional circumstances, a life-preserving donation from an infected donor may be released for clinical use in a recipient who also is infected with or has cleared HCV in accordance with Section 10. In exceptional circumstances a life-preserving donation from a donor whose serum is concordantly repeatably reactive for, or contains, anti-HCV may be released for clinical use providing HCV RNA is undetectable, bearing in mind that this does not absolutely exclude infectivity. Consider seeking expert advice concerning HCV management in recipient.

*** Partner donation of washed sperm for IUI and IVF may be considered in exceptional circumstances.

Human T cell Leukaemia Virus (HTLV)

9.19 Screening for HTLV infection employs an antibody-only assay;

9.20 Samples giving repeat reactivity should undergo confirmatory testing as soon as possible. The detection of confirmed anti-HTLV indicates current infection. Reference NAT testing may be used to confirm HTLV infection;

9.21 In exceptional circumstances a life-preserving donation from a repeat reactive donor may be released for clinical use providing the antibody reactivity is shown to be non-specific in confirmatory testing and HTLV genome is not detected by reference NAT.

Table 9 – The interpretation of a repeatably-reactive serological result in an ALLOGRAFT donor – HTLV

Test result(s) suggesting possible donor HTLV 1/ 2 infection	Organs	Tissues	HPC and TC	Reproductive cells	Human embryonic stem cells
Anti-HTLV 1/2	Contraindication to donation*	Contraindication to donation*,**	Contraindication to donation	Contraindication to donation	Contraindication to donation

* The immunosuppression associated with organ transplantation significantly increases the risk of disease by accelerating presentation of HTLV-related illness. The use of donations from an HTLV-infected donor in a recipient who will require immunosuppression should be avoided.

** See paragraph 8.13 for possible derogation.

Treponema pallidum (Syphilis)

9.22 Syphilis infection is detected by screening for specific antibody to *T. pallidum* or by the use of non-specific tests such as Wasserman reaction;

9.23 Samples giving repeat reactivity in the screening assay should undergo confirmatory testing as soon as possible. The detection of confirmed anti-*T. pallidum* antibody indicates past or current infection;

9.24 Unrelated candidate HPC/TC donors whose serum contains antibody to *T. pallidum* are usually deferred for 5 months following recovery (Guidance from the World Marrow Donor Association (WMDA) can be found here and here). Initial or repeat reactivity in a non-specific screening test does not exclude donation if the donor sample is un-reactive in *T. pallidum* specific assays.

Table 10 – The interpretation of a repeatably-reactive serological test result in an ALLOGRAFT donor – *Treponema pallidum*

Test result(s) suggesting possible syphilis infection of donor	Organs	Tissues	HPC and TC	Reproductive cells	Human embryonic stem cells
***T. pallidum* antibody or non-specific assays such as WR**	Donation permitted*	Contraindication to donation**	Donation permitted*	Contraindication to donation	Contraindication to donation**

* Where a recipient has been exposed to a potentially infectious donation a risk assessment of the potential for transmission should be undertaken. If transmission is considered a possibility, expert advice should be sought from a genitourinary physician to ensure administration of adequate antimicrobial therapy and the patient should be monitored for serological evidence of syphilis infection.

** In exceptional circumstances a donation from a repeat reactive donor or a donor whose serum contains antibody may be released as above for clinical use.

Cytomegalovirus (CMV)

9.25 CMV causes lifelong infection. Organs, stem cells and tissues containing viable cells from a seropositive donor transmit CMV infection and may cause severe CMV disease in a susceptible recipient. CMV disease may also be due to reactivation of latent virus in seropositive recipients;

9.26 Ideally seronegative transplant or HPC/TC recipients should receive a donation from a seronegative donor. If the donor and/or recipient is seropositive, routine CMV prophylaxis should be administered post-transplant and/or routine CMV viral load surveillance instituted. The use of sperm from a CMV seropositive donor is not contra-indicated;

9.27 Neonates (<1.5kg birth weight) and immunocompromised recipients are at greatest risk of CMV disease;

9.28 Anti-CMV identifies risk but does not accurately predict transmission.

Table 11 – The interpretation of a repeatably-reactive serological result in an ALLOGRAFT donor – CMV

Test result(s) suggesting possible donor CMV infection	Organs	Tissues	HPC and TC	Reproductive cells	Human embryonic stem cells
Anti-CMV	Donation permitted. Informs need for post transplant CMV monitoring	Donation permitted. Informs need for post transplant CMV monitoring	Donation permitted. Informs need for post transplant CMV monitoring. Match serology status if possible	Match serology status to donor if possible	CMV DNA positive unsuitable for use*

* All umbilical cord donations are tested prior to issue by CMV NAT. In exceptional circumstances a life preserving donation containing CMV DNA might be used for a donor whose serum contains anti-CMV in accordance with Section 10. Routine CMV prophylaxis should be administered post-transplant and/or routine CMV viral load surveillance instituted.

Toxoplasma gondii

9.29 Organs and solid tissues which contain tissue cysts from an infected donor may represent a risk of primary infection and disease in a naïve and immunosuppressed recipient; post transplant prophylaxis should be considered.

Table 12 – The interpretation of a repeatably reactive serological result in an ALLOGRAFT donor – *Toxoplasma gondii*

Test result(s) suggesting possible *T. gondii* infection of donor	Organs*	Tissues	HPC and TC**	Reproductive cells	Human embryonic stem cells
Anti-*T. gondii* IgG; and IgM for HPC/TC donors only	May inform need for prophylaxis in heart recipients	Donation permitted	Informs need for prophylaxis and donor deferral if recent acute infection	Not required	Not required

* The risk of acquiring *T. gondii* infection from the transplant, rather than developing *T. gondii* disease from endogenous reactivation in the recipient under immunosuppression, results from a serological mismatch between an infected donor (antibody positive) and a naïve seronegative recipient.

** Avoid donors with evidence of recent/acute infection (e.g. IgM positive) – WMDA guidelines suggest 6 month deferral after acute infection. Recently or acutely infected donors may have a parasitaemia with the presence of trophozoites in the peripheral blood. While IgM antibody provides an indication of recent/acute infection this antibody may persist for significantly longer than 6 months. If delay in transplantation may result in significant clinical risk to the recipient, further testing, including NAT testing and IgG avidity, may be helpful in determining the duration of infection in the donor and informing a risk and benefit analysis.

Epstein-Barr virus (EBV)

9.30 EBV causes a persistent infection, and organs, HPC and TC from an EBV seropositive donor may transmit infection. EBV may also reactivate in sero-positive recipients;

9.31 Post transplant acute EBV infection in an immunosuppressed naïve recipient carries with it the significant risk of Post Transplant Lymphoproliferative Disease (PTLD) which can prove fatal. Where primary EBV infection / reactivation is considered a possibility, close monitoring of EBV DNA levels is advisable.

Table 13 – The interpretation of a repeatably-reactive serological result in an ALLOGRAFT donor – EBV

Test result(s) suggesting possible EBV infection of donor	Organs	Tissues	HPC / TC	Reproductive cells	Human embryonic stem cells
Anti-EBV	Donation permitted. Informs need for post transplant EBV monitoring. Match recipient status if possible, especially in children.	Donation permitted. Informs need for post transplant EBV monitoring.	Donation permitted. Informs need for post transplant EBV monitoring*	Not required.	Not required.

* It is advisable to avoid donors with evidence of acute infection

Transmissible Spongiform Encephalopathies (TSEs)

9.32 TSEs (otherwise known as prion diseases) are a group of fatal transmissible neurodegenerative disorders that in humans occur in sporadic, genetic and acquired forms. The commonest human TSE, Creutzfeldt-Jakob disease, occurs in both sporadic (sCJD) and acquired (vCJD) forms. The transmissible agent (or prion) is composed principally of a misfolded host protein, the prion protein, that accumulates at high levels in the brain.

9.33 Over past decades, sCJD has been transmitted from one patient to another through medical or surgical procedures involving neurosurgical instruments, brain electrodes, tissue (human cornea and dura mater grafts) and tissue extracts (human pituitary hormones). There have been no known transmissions of vCJD via surgery or use of tissues or organs to date; however there has been transmission of vCJD infection via transfusion of red blood cells (4 cases) and UK plasma used to produce Factor VIII (1 case).

9.34 Donor deferral issues centre around the potential for transmitting TSEs during organ and tissue transplantation. Deferral of donors is complex. An effective screening test for the detection of misfolded prions in donor blood is not available at present, and the prevalence of asymptomatic infected persons in the UK is uncertain.

9.35 However, there are a number of risk factors for human TSEs that have been identified, including prior exposure to human blood, dura mater grafts, pituitary-derived hormones and contaminated surgical instruments. In addition, a number of individuals have been notified that they are at increased risk of CJD/vCJD for public health purposes, due to their exposure to one or more risk factors. Guidance from the Advisory Committee on Dangerous Pathogens' TSE Working Group is available from their website and information on notifications is on the CJD Incidents Panel website.

9.36 Individuals with a confirmed or suspected TSE, a neurological disease of unknown aetiology or those who are blood relatives of persons with familial CJD cannot be accepted as donors of organs or tissues. However, if a donor has had two or more blood relatives develop a prion-associated disease and, following genetic counselling, they have been informed they are not at risk, they may be accepted for donation.

9.37 Pre-exposure to human dura mater grafts, human pituitary-derived growth hormone and/or gonadotrophin excludes the donation of tissues, and should be taken into account when assessing any donor for their suitability for organ donation. There is no good evidence of transmission by organs or tissues other than by those of the central nervous system.

9.38 For lifesaving organ and bone marrow transplantation only, donor exposure to risk factors for CJD and vCJD should be taken into account in the risk assessment, but does not necessarily preclude donation.

9.39 Table 14 gives a summary of the exclusions from organ and/or tissue donation, based on possible TSE exposure.

Table 14 – Exclusions from organ and/or tissue donation based on possible TSE exposure

	LIVE TISSUE DONORS		CADAVERIC TISSUE DONORS				SOLID ORGAN DONORS
	Bone	**HSC**	**Musculoskeletal (ligaments, tendons & cartilage)**	**Bone and processed bone**	**Ocular**	**Skin/ Heart Valves**	
Definite, probable or possible case of human TSE, including CJD and vCJD	Exclude	Exclude	Exclude	Exclude	Exclude	Exclude	Exclude
Individual with a neurological disease of unknown aetiology	Exclude	Exclude	Exclude	Exclude	Exclude	Exclude	Exclude
Individual whose blood relatives have had familial CJD [1]	Exclude	Exclude	Exclude	Exclude	Exclude	Exclude	Exclude
Individual "presumed infected" with vCJD [2]	Exclude	Exclude	Exclude	Exclude	Exclude	Exclude	Exclude
Individual "at increased risk of CJD/vCJD" (for public health purposes) [3]	Exclude	Individual assessment required [4]	Exclude	Exclude	Exclude	Exclude	Individual assessment required [4]
History of definite [5] or probable [6] blood transfusion since 1980	Exclude	Individual assessment required [4]	Exclude Do not exclude if transfusion is within 1 week prior to death	Exclude	Do not exclude [7]	Do not exclude	Individual assessment required [4]
History of receipt of *dura mater* graft	Exclude	Individual assessment required [4]	Exclude	Exclude	Exclude	Exclude	Individual assessment required [4]
History of definite receipt of tissue since 1980	Exclude	Individual assessment required [4]	Exclude	Exclude	Exclude	Do not exclude	Individual assessment required [4]

History of receipt of pituitary derived growth hormone and/or gonadotrophin	Exclude	Individual assessment required [4]	Exclude	Exclude	Exclude	Exclude	Individual assessment required [4]
History of receipt of organ	Exclude	Exclude	Exclude	Exclude	Exclude	Exclude	Individual assessment required [4]

[1] However, if a donor has had two or more blood relatives develop a prion-associated disease and, following genetic counselling, they have been informed they are not at risk, they may be accepted for donation

[2] Donors who have received blood components, tissues and/or organs from donors who have gone on to develop vCJD.

[3] Donors who have been notified that they are at increased risk of vCJD (for public health purposes) due to possible exposure.

[4] Level of risk or exposure should be clarified and weighed, on an individual basis, against the expected benefit of the transplant and the availability of alternative donors. The recipient (and/or relatives) should be informed of the nature of the estimated risk of vCJD transmission.

[5] Definite transfusion is defined as at least one of the following:

- Recorded in medical notes available to clinical staff at time of donation;
- Documented during interview;
- Reported by GP;

[6] For tissue and organ donors, probable transfusion is defined as:

- previous major surgery; and/or
- previous major accident.

[7] Ocular donors should not be excluded if they have a history of definite or probable transfusions, in view of supply issues. However it is essential that:

- information is provided to recipients;
- wherever possible donor and recipients are age matched;
- efforts are made to increase yields of ocular tissues;
- donors excluded on the basis of public health measures are not accepted as ocular donors.

Other infections in organ and tissue donors

9.40 At the time a deceased donor is being considered for suitability there may be a number of other or even co-incidental infections which may have a bearing on safety. Diagnosed acute infections, and undiagnosed presumed acute infectious disease, in a potential donor do not necessarily preclude donation, but any such illness should be discussed with the local consultant microbiologist/virologist.

9.41 A full listing for tissues which draws on blood donor safety is available in Chapter 22 of the Guidelines for the Blood Transfusion Services. We lay out below a synopsis of relatively common conditions which reflect recurrent problems. **This section does not apply to HPC/TC donors.**

Bacterial meningitis

9.42 If bacterial meningitis has been confirmed, but there is no visible damage or local infection in the organ or tissues required at retrieval, the donation of the organs, tissues and cells are acceptable.

9.43 Appropriate antibiotic prophylaxis covering any organism isolated from the donor should be considered for identifiable recipients, especially in the case of organs.

9.44 Material from meningitis cases from whom no organism is cultured should not be used for donation.

9.45 Expert advice should be obtained.

Viral meningo-encephalitis

9.46 The aetiology of fatal viral encephalitis is difficult to establish.

9.47 If there is any possibility of acquisition of a neurotropic infection from abroad the donation is contraindicated owing to the risk of rabies, West Nile virus or other exotic neurotropic infections.

9.48 If herpes simplex virus (HSV) or varicella zoster virus (VZV) CNS infection is diagnosed as a manifestation of systemic viral infection (as seen in neonates and the immunosuppressed), donation of organs, tissues and cells is contraindicated as the viruses may be disseminated widely with associated viraemia.

9.49 HSV encephalitis without evidence of systemic infection can be treated with antiviral therapy and the likelihood of disseminated infection in the donor is small, even without antiviral therapy. In this situation antiviral prophylaxis should be considered for the recipient.

9.50 Organs can be considered for donation if local HSV/VZV infection has been treated with adequate antiviral therapy for >7 days; if treated <7 days, the recipient should receive antiviral prophylaxis. Serological status of the recipient may also inform a risk and benefit analysis.

9.51 Eyes must not be donated if the donor has a past history of, or active infection with, either HSV or VZV.

9.52 Material from cases of meningo-encephalitis for which no infection is identified should not be used for donation.

9.53 Expert microbiological advice should be obtained.

Influenza

9.54 Lungs and bowel should not be used from donors with confirmed influenza infection.

9.55 Other organs may be offered, and the final decision lies with the transplanting surgeon weighing the balance of risks for the recipient. Death from influenza has been associated with the demonstration of viral presence in organs and tissues outside the respiratory tract. Pathogenicity of some strains of virus may be enhanced by the co-incidental immunosuppression implicit in transplantation.

9.56 SaBTO has issued advice concerning organ donation and seasonal influenza.

Tuberculosis

9.57 Donation of organs, tissues and cells is contraindicated from donors with active disease or within the first six months of anti-tuberculosis treatment.

9.58 However, organs can be considered for transplant if a recipient has received a 6 month course of chemotherapy, unless the isolate is found to be resistant to appropriate anti-tuberculous drugs.

9.59 If there is a past history of tuberculosis at the site of the organ to be used for donation, use of that organ is contraindicated but the donation of other organs is acceptable.

Bacteraemia

9.60 Where an organ donor has been diagnosed with bacteraemia in the 5 days preceding the donation but there is no visible damage or local infection in the organ at retrieval, donation of an organ is acceptable with appropriate recipient antibiotic prophylaxis.

9.61 Tissues should not be retrieved from a donor who has been found to be bacteraemic until 14 days after clinical recovery. If the microbiological view is that the bacteraemia was likely to be incidental and is unlikely to represent a hazard to the recipient, tissues may be retrieved.

9.62 Bacteraemia is not considered a contraindication for corneal donation provided the corneas are stored by organ culture at 31^{o}C-37^{o}C where there is a greater opportunity to detect bacterial contamination and where the antibiotics in the organ culture medium are more effective than under cold storage conditions.

Abscesses

9.63 Organ donors with abscesses occurring in the preceding 5 days and at a distance from the organ to be retrieved are acceptable for donation if appropriate recipient antibiotic prophylaxis covering the causative organism is given;

9.64 *Staphylococcus aureus* and *Streptococcus pyogenes* are more likely to spread to distant organs and cause infection in a recipient;

9.65 An abscess caused by local spread of an organism other than staphylococci or streptococci may have no impact on a distant organ, and in these circumstances the recipient may not require antibiotics. Transmission of infection is also unlikely after drainage of an abscess and adequate treatment of the donor;

9.66 If the clinician caring for the potential donor believes that therapy given for a localised infection has successfully cleared the infection, tissues may be retrieved. Otherwise, the donation of tissues and cells is contraindicated unless life-preserving.

MRSA

9.67 In recent years community-acquired methicillin resistant *S. aureus* (MRSA) infections have emerged as a significant clinical problem, and are commonly associated with skin and soft tissue infections. Donations of skin which are positive for *S. aureus* should not be released for transplantation unless they are effectively sterilized by a process such as gamma irradiation at a target absorbed dose of 25 kGy.

Malaria

9.68 The donation of organs, tissues (other than corneas) and cells from donors with active malarial infection and no curative chemotherapy is contraindicated. Corneal tissue, but not other ocular tissue, is acceptable as corneas are avascular and not considered to be a risk of transmitting protozoal infections;

9.69 Patients with a history of travel to a malaria-endemic area, but afebrile at the time of assessment, can be accepted as donors at one year or longer since return to the UK;

9.70 If return to the UK is between 6 months and 1 year, a validated anti-malarial antibody test should be performed. Organs may be used before the serological result is available. If a positive result for malarial antibodies is reported after transplantation has taken place, a risk analysis should be carried out and follow up of the recipients undertaken;

9.71 If the return to the UK is within 6 months defer the living donor. For deceased donors the organs may be used but a validated malarial antibody test of the donor should be done and follow up of the recipients undertaken irrespective of the donor antibody status;

9.72 Febrile donors with a recent travel history require a malarial screen (blood film and PCR) before donation;

9.73 Irradiation at 25 kGy dosage offers a method for tissue sterilisation for those tissues able to withstand this process and offers an alternative to malarial antibody testing of donors with a travel history;

9.74 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 donation may proceed pending the results. In very special circumstances e.g. where the donor is the only match for a bone marrow transplant, expert advice should be sought to inform a risk assessment;

9.75 When a recipient has been found to have received a donation from a donor whose serum contains malarial antibody, a risk analysis must be undertaken with the assistance of the HPA Malaria Reference Laboratory. This will require testing for the presence of malarial parasitaemia in both the donor and the recipient. The recipient should be advised of the potential risk of contracting malaria and clinicians should consider the diagnosis if the recipient subsequently becomes ill with pyrexia.

Fungal infection

9.76 Organs, tissues and cells from donors with superficial fungal infection of the skin or mucosa (thrush) are acceptable for donation;

9.77 Organs from a patient with a blood stream infection or abscess due to *Candida* spp. are acceptable for donation providing appropriate recipient antibiotic prophylaxis covering the donor organism is given;

9.78 Aspergillosis or other systemic fungal infections are contraindications for organ transplantation unless a specific risk assessment is carried out and appropriate recipient antifungal prophylaxis is prescribed;

9.79 All tissues and cells from donors with systemic fungal infections are contraindicated for donation.

Unusual bacterial/fungal/protozoal infections

9.80 Expert microbiological advice should be sought when considering using organs, tissues or cells from donors who have had unusual infections in the past, including those acquired outside of Western Europe. This should include infections common in immuno-compromised patients (e.g. listeriosis, nocardiosis) or infections which lie dormant or are difficult to eradicate (e.g. brucellosis, Lyme disease, typhoid).

Chagas Disease

9.81 *Trypanosoma cruzi* infection is becoming apparent in Latin American migrants to the UK. Donors who:

- were born in South America or Central America (including Southern Mexico); or
- whose mothers were born in these countries; or,
- who may have been transfused with blood in these countries; or
- who have lived and/or worked in rural subsistence farming communities in these countries for a continuous period of 4 weeks or more;

should not donate tissues, other than corneas, or organs unless they have been shown by a validated test for *T. cruzi* antibody not to have antibody in their blood. For this to be valid the test must have been performed at least 6 months following the date of last potential exposure.

10. Exceptional use of organs and tissues from donors potentially or known to be infected

Derogation of exclusion criteria for donors who carry an infection risk

10.1 We acknowledge the overwhelming clinical need for, and shortage of, organs suitable for transplantation in the UK. The loss of potential organs needs to be avoided at all times and has been addressed in part by the guidelines for testing described above.

10.2 We accept that there may be clinical need for transplantation of such urgency that it may be appropriate to consider the use of organs and tissues for life-preserving purposes from donors who would not otherwise be considered eligible to donate, due to a known or perceived infection risk. Potential organs from such donors should be offered to the transplant community. Fully informed consent to such a procedure is required from the recipient of such transplantation and all measures for risk reduction, including onward transmission, must be taken. Transplants of this nature are likely to be infrequent. Intensive immediate post-transplant monitoring and long-term follow-up of the infection status of recipients should be set in place and the long-term outcome of the recipient recorded centrally by the transplant community.

Matching infection status of donor and recipient

10.3 Usually any reactivity in one or more of the mandatory marker assays used for screening donors renders the donor ineligible and the potential donations unsuitable for use without any leave to alter this decision. This is exemplified by the protocols surrounding the practice of blood transfusion and the exclusion of "risk donors". In principle the same applies to any donor of tissues and organs although, as we discuss below, in truly life-preserving situations, relaxation or even derogation of this exclusion may be possible, in particular in situations of discordant serological results in the donor.

10.4 Where a donor sample repeat reactive in one assay is un-reactive in one or more assays of similar sensitivity the likelihood of subsequent confirmatory testing indicating this reactivity to be specific is very low. If testing laboratories have evidence based validated SOPs which indicate such discordant reactivity is likely to be non-specific, only then can consideration be given to disregarding the discrepant repeat reactivity in terms of allowing donation.

10.5 On the rare occasion when a life-preserving transplant is required urgently, it may be appropriate to consider the use of an organ from a donor who is known to be infected, or who is potentially infected, including those whose serum is discordantly repeat reactive in a serological test. For example, it is possible to envisage the use of a heart from a donor known to be infected with HCV or HIV for a critically ill recipient in the terminal stages of circulatory failure who is also infected with HCV or HIV (i.e. infection match). Such situations are likely to occur infrequently but represent an extreme example of the necessary balancing of the risk versus benefit analysis which should be considered in every case where transplantation is under consideration.

10.6 Previous infection, current infection or immunisation may decrease or remove the risk of infection following the use of a transplant from a donor who is known to be infected, or who is potentially infected. This approach involves matching of the immune status of the recipient to the infection status of the donor. For example a recipient shown to be immune to hepatitis B, naturally or by immunisation, is unlikely to suffer re-infection should the transplant be taken

from an HBV-infected donor. In this type of matching it is essential that the status of the recipient be known with absolute certainty.

10.7 Matching the status will also include an assessment of the likelihood of transmitting viral phenotypes which may pose an additional hazard to the already-infected recipient including viruses of increased pathogenicity, drug resistant variants, immune escape variants and a number of co-infections such as hepatitis delta virus and herpes virus 8. Specialist microbiological/virological support should be sought to ensure that appropriate testing has been undertaken in the correct manner and within the available time to inform the risk assessment and to confirm the recipient's status.

Balancing risk and benefit

10.8 In general, derogation of the exclusion of infected donors should only be considered when the donation is truly considered to be life-preserving. In this situation the transplant surgeon should, with the informed consent of the potential recipient, balance the risk of infection against the risk of dying whilst waiting for another graft.

10.9 Heart, lung and liver transplants will almost always fit within this definition, generally because the clinical situation of the recipient requiring these organs is likely to be one of incipient death. Other solid organs and some very specialised tissues such as haematological stem cells may also fulfil this definition. Other tissues are unlikely to do so but exceptions may occur.

10.10 Where, however, short-term or intermediate support measures can be employed to avoid the immediate need for transplantation, and where there is a reasonable expectation of future availability of an appropriate organ, the balancing of risk and benefit may favour delaying the transplantation of a high infection risk donation.

Risk mitigation

10.11 Specialist advice should be sought, especially over the provision of prophylaxis for the recipient. The use of pre-exposure prophylaxis involving antiviral drugs or antibiotics may be appropriate. Counselling will require a discussion of the potential infection risk and the possibility of disease arising from infection.

10.12 Prophylaxis for partners and all family members including active immunisation, antimicrobial drugs and advice over the routes of transmission (sexual and social) must be given in order to reduce the risks of secondary transmission.

10.13 In the immediate post transplant period comprehensive surveillance for infection of the recipient will be required with interventions planned should they become necessary in the face of active infection.

The offering, collection and use of organ donations carrying infection risks

10.14 Guidelines on the suitability for donation are issued by the Organ Donation and Transplantation directorate of NHSBT. However, where a potential donor is found by laboratory screening to be infected, or possibly be infected, with a significant microbial agent, the Specialist Nurse-OD should still consider offering life-preserving organs to ODT and the transplant community.

10.15 The decision to use such organs or tissues ultimately lies with the transplant surgeon and team and must only be taken with the express permission and informed consent of the

recipient or, where this is not possible, of the recipient's partner or if not, of the next of kin. These decisions and permissions must be recorded.

10.16 Expert microbiological advice should be sought and any recommendations recorded in the patient's notes.

10.17 The retrieval team should be made aware of the potential hazards of organ retrieval where the donor is known to be infected, and appropriate control of infection procedures and risk reduction measures should be undertaken during organ retrieval. This may include appropriate personal protective equipment (PPE) as required.

10.18 Any pre-transplant manipulation of the donation, either at the time of retrieval or at the time of transplantation must also be carried out observing the appropriate containment and risk reduction procedures relevant to the infection risk. They should include appropriate site terminal decontamination.

10.19 Organs for transplantation taken from infected or potentially infected donors must be appropriately labelled for transplantation as normal but in addition, where third-party contact with the donation could lead to a risk of infection, the external packaging should clearly be marked with "infection risk" and carry the appropriate UN hazard labelling. Internal labelling must clearly state the nature of the infection risk.

10.20 Samples from a donor who is known to be infected, or who is potentially infected, similarly will carry a risk for the receiving analytical laboratories. However, since laboratories associated with transplantation activity will also be receiving unscreened patient materials as part of their service, it is important that they have in place laboratory practices designed to allow safe handling of any patient materials, irrespective of the infection status. Where laboratory procedures are deemed to give rise to unacceptable risks with known blood-borne virus infections these procedures should either be moved to a suitable containment facility or modified to reduce hazards for the analysis of all samples, irrespective of the known infection status of the samples. Analytical laboratories unable to comply with these recommendations should consider whether they have appropriate facilities for handling human materials.

11. Adverse incidents relating to transplantation

11.1 In view of the time pressures implicit in organ transplantation, and the possibility of a multi-organ donor also being a tissue donor, laboratory testing of tissues may identify an infection risk to recipients of organs that have already been transplanted. It is also possible that an adverse incident arising from an organ transplant may identify an infectious risk not known at the time tissues were retrieved. There are cases of viral transmission described in the literature which could have been prevented had an adverse event in an organ recipient been linked appropriately to involved tissues from the same donor.

11.2 As a matter of principle for effective surveillance, there is value in the clinician looking after a surviving recipient considering the routine screening of recipients at one year follow-up from transplantation for microbial infection potentially transmitted from the donor to the recipient. In view of transplant-associated immunosuppression, NAT testing may be indicated. The availability of a pre-transplantation sample from the recipient may often be very valuable in the investigation of cases of potential transmission.

11.3 In the situation where an infection in an organ transplant recipient indicates potential transmission from the donor, it is the duty of the clinician looking after the organ transplant recipient to ensure that other recipients of organs from the same donor, the involved Specialist Nurse-OD and Tissue Establishments are notified as soon as possible and made aware of the potential infection risk. The Duty Office at the Directorate for Organ Donation and Transplantation, NHSBT is in a position to assist in ensuring that all relevant clinicians are informed. The involved Tissue Establishment must undertake a risk assessment of involved tissues held in their inventory or, where these have been issued to users, contact the users and undertake a tissue recall. The designated individual has a responsibility to ensure that HTA SAEARs is informed (see paragraph 11.6 below).

11.4 Where a potential for transmission exists, appropriate follow-up of all recipients must be undertaken:

- It is essential that confirmatory testing, including NAT assays, be undertaken on the donor sample to confirm specificity of the serological reactivity and the likelihood of transmission;
- A risk assessment should be undertaken to identify the susceptibility of the recipient to infection and to disease;
- Expert advice should be sought and appropriate post-exposure prophylaxis administered to the recipient;
- Prophylaxis should also be considered for close contacts of the recipient where secondary transmission is possible;
- The exposed recipient should be enrolled for follow-up;
- It is good medical practice to refer an infected living donor and close contacts of any infected donor, living or deceased, to an appropriate expert.

11.5 Secure systems are in place for reporting the adverse outcome of treatment with blood and blood components (SHOT and SABRE), and similar care should be taken to report serious adverse incidents arising out of transplantation. Tissue establishments are legally obliged to report Serious Adverse Reactions and Serious Adverse Events to their Competent Authority (see paragraph 11.6 below). Once the 2010 EC Directive “Standards of quality and safety of

human organs intended for transplantation" (2010/53/EU) has been applied in the UK, a similar requirement will apply to organ establishments.

11.6 For the purposes of reporting, a Serious Adverse Reaction is defined as an unintended response, including a communicable disease, in the donor or in the recipient associated with the procurement or human application of tissues and cells that is fatal, life-threatening, disabling, incapacitating or which results in, or prolongs, hospitalisation or morbidity. A Serious Adverse Event is defined as any untoward occurrence associated with the procurement, testing, processing, storage and distribution of tissues and cells that might 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.

11.7 HTA licensed establishments in the UK are required to report adverse events to the HTA through the Serious Adverse Events and Reactions system (SAEARs). The HTA then reports these to the European Commission. This process follows guidelines established by the European Union Standards and Training in the Inspection of Tissue Establishments working group.

11.8 In the case of tissue donors, many donations increasingly cross national boundaries. The mandated requirement to inform Competent Authorities of adverse reactions will allow other Competent Authorities (UK or otherwise) to be informed.

11.9 For ACUs, relevant guidance is given in note 27 of the HFEA Code of Practice.

12. References

Reference	Link
Advisory Committee on Dangerous Pathogens TSE Working Group guidance	http://www.dh.gov.uk/ab/ACDP/TSEguidance/index.htm
Advisory Committee on the Safety of Blood, Tissues and Organs	http://www.dh.gov.uk/ab/SaBTO/index.htm
Cellular Therapy Standards – FACT (Foundation for the Accreditation of Cellular Therapy)	http://factwebsite.org/ctstandards/
Directive 2004/23/EC Setting standards of quality and safety for the donation, procurement, testing, processing, preservation, storage and distribution of human tissues and cells	http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2004:102:0048:0058:en:PDF
Directive 2006/17/EC Implementing Directive 2004/23/EC of the European Parliament and of the Council as regards certain technical requirements for the donation, procurement and testing of human tissues and cells	http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2006:038:0040:0052:EN:PDF
Directive 2006/86/EC Implementing Directive 2004/23/EC of the European Parliament and of the Council as regards traceability requirements, notification of serious adverse reactions and events and certain technical requirements for the coding, processing, preservation, storage and distribution of human tissues and cells	http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2006:294:0032:0050:EN:PDF
Directive 2010/53/EU Standards of quality and safety of human organs intended for transplantation	http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2010:207:0014:0029:EN:PDF
European Union Standards and Training in the Inspection of Tissue Establishments working group	http://www.eustite.org/
Guidance notes on the processing, storage and issue of bone marrow and blood stem cells – Department of Health 1997	http://www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_4006584
Guidelines for the Blood Transfusion Services in the UK	http://www.transfusionguidelines.org.uk/index.aspx?Publication=RB

HTM 07-01 – Safe management of healthcare waste – Department of Health	http://www.dh.gov.uk/prod_consum_dh/groups/dh_digitalassets/documents/digitalasset/dh_073328.pdf
Human Fertilisation and Embryology Act 1990 2008 amendment	http://www.legislation.gov.uk/ukpga/1990/37/contents http://www.legislation.gov.uk/ukpga/2008/22/contents/enacted
Human Fertilisation and Embryology Authority (HFEA)	www.hfea.gov.uk
Human Fertilisation and Embryology (Quality and Safety) Regulations 2007	http://www.legislation.gov.uk/uksi/2007/1522/contents/made
HFEA Code of Practice	http://www.hfea.gov.uk/code.html
HFEA Directions	http://www.hfea.gov.uk/188.html
Human Tissue Act 2004	http://www.legislation.gov.uk/ukpga/2004/30/contents
Human Tissue (Scotland) Act 2006	http://www.legislation.gov.uk/asp/2006/4/contents
Human Tissue Authority (HTA)	www.hta.gov.uk
Human Tissue (Quality and Safety for Human Application) Regulations 2007	http://www.legislation.gov.uk/uksi/2007/1523/contents/made
HTA Codes of Practice	http://www.hta.gov.uk/legislationpoliciesandcodesofpractice/codesofpractice.cfm
HTA Directions	http://www.hta.gov.uk/legislationpoliciesandcodesofpractice/htalegaldirections.cfm
SHOT	http://www.shotuk.org/home/
SABRE	http://www.mhra.gov.uk/Safetyinformation/Reportingsafetyproblems/Blood/index.htm
World Marrow Donor Association International Standards for Unrelated Hematopoietic Stem Cell Donor Registries	http://www.worldmarrow.org/fileadmin/WorkingGroups_Subcommittees/Accreditation/Documents/standards_history/WMDA_Standards-version_November_2008_01.pdf
Haematopoietic stem cell donor registries: World Marrow Donor Association recommendations for evaluation of donor health. *Bone Marrow Transplantation* (2008), 1–6	http://www.worldmarrow.org/fileadmin/Education/Publications/bmt200876a.pdf
UK Stem Cell Tool Kit	http://www.sc-toolkit.ac.uk/home.cfm

13. Abbreviations

A&E	Accident and Emergency
ACDP	Advisory Committee on Dangerous Pathogens
ACU	Assisted Conception Unit
Anti-HBc	Hepatitis B core antibody
Anti-HBs	Hepatitis B surface antibody
ATMPs	Advanced therapeutic medicinal products
BSE	Bovine Spongiform Encephalopathy
CMV	Cytomegalovirus
CNS	Central Nervous System
CPA	Clinical Pathology Authority
CJD	Creutzfeldt-Jakob Disease
DBD	Donation after brain death (previously heart beating donor)
DCD	Donation after cardiac death (previously non heart-beating donors)
DNA	Deoxyribonucleic acid
EBV	Epstein Barr virus
EDTA	Ethylene diaminetetracetic acid
EU	European Union
EUSTITE	European Union Standards and Training in the Inspection of Tissue Establishments Working Group
EUTCD	European Union Tissue and Cells Directives
FACT	Foundation for the Accreditation of Cellular Therapy
GIFT	Gamete Intrafallopian Transfer
GP	General Practitioner
HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HCV Ag	Hepatitis C antigen
hESCs	Human embryonic stem cells
HFEA	Human Fertilisation and Embryology Authority
HHV8	Human herpes virus 8
HIV	Human immunodeficiency virus
HPA	Health Protection Agency
HPA NIBSC	National Institute of Biological Standards and Controls
HPC	Haemopoetic progenitor cells
HSC	Haemopoetic stem cells

HSE	Health and Safety Executive
HSV	Herpes simplex virus
HTA	Human Tissue Authority
HTLV	Human T cell Leukaemia virus
IA	Independent assessor
ICSI	Intracytoplasmic sperm injection
IgG	Immunoglobulin G
IgM	Immunoglobulin M
iPS	Induced pluripotent stem cells
IR	Initial reactive
ISO9001	International Organisation for Standardisation, Quality Management Systems – Requirements
IUI	Intrauterine Insemination
IU	International Units
IVF	In-vitro fertilisation
kGy	Kilo-Greys
MHRA	Medicines and Healthcare products Regulatory Agency
MRSA	Methicillin-resistant *Staphylococcus aureus*
MSBTO	Advisory Committee on the Safety of Microbiological Safety of Blood, Tissues and Organs
MSM	Men who have sex with men
NAT	Nucleic acid amplification technology
NHS	National Health Service
NHSBT	NHS Blood and Transplant
ODR	NHS Organ Donor Register
ODT	Organ Donation and Transplantation Directorate of NHSBT
PA1	NHS Blood and Transplant Patient Assessment form
PCR	Polymerase Chain Reaction
PPE	Personal Protective Equipment
PrP	Prion related protein
PTLD	Post Transplant Lymphoproliferative Disease
RNA	Ribonucleic acid
RR	Repeat reactive
SABRE	Serious Adverse Blood Reactions and Events
SaBTO	Advisory Committee on Safety of Blood Tissues and Organs
SAEARs	Serious Adverse Events and Reactions system (HTA)
SHOT	Serious Hazards of Transfusion

SOP	Standard Operating Procedure
TC	Therapeutic cells
TSE	Transmissible Spongiform Encephalopathy
UK	United Kingdom
UKAS	United Kingdom Accreditation Service
UN	United Nations
vCJD	Variant CJD
VZV	Varicella zoster virus
WMDA	World Marrow Donor Association
WR	Wassermann Reaction for Syphilis

Annex 1: Members of Working Group

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