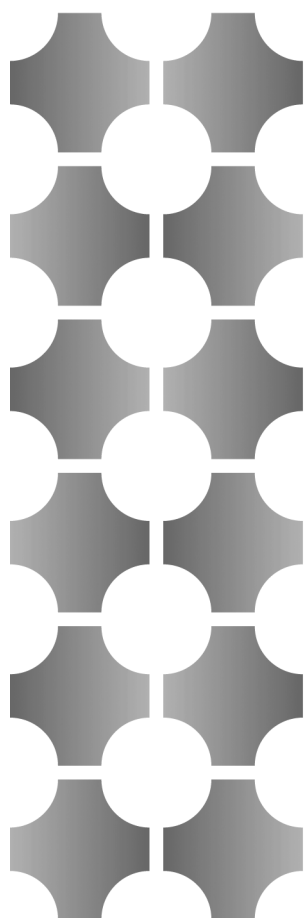


Guidelines for the **Blood Transfusion Services in the United Kingdom**

7th Edition 2005

Addendum



London: TSO

Contents

Preface	v
Tables	vi
Change notifications	vii
Chapter 21 Tissue banking: general principles	1
Chapter 22 Tissue banking: selection of donors	5
22.1 General considerations	5
22.2 Consent	6
22.3 Medical and behavioural history	7
22.4 Tissue-specific donor considerations	8
22.5 Donor testing	8
22.6 Testing of living donors	9
22.7 Testing of deceased donors	9
22.8 Follow up	10
22.9 Autologous tissue donation	10
22.10 Archiving of donor samples	11
22.11 Release criteria	11
Chapter 23 Tissue banking: tissue retrieval and processing	13
23.1 General considerations	13
23.2 Retrieval	14
23.3 Transportation conditions	15
23.4 Bacteriostasis and disinfection	15
23.5 General guidelines for tissue processing	15
23.6 Tissue storage	19
23.7 Tracking of tissues	21
23.8 Notification of serious adverse events and reactions	22
23.9 Additional guidelines for skeletal tissue retrieval and processing	23
23.10 Cardiovascular tissue retrieval and processing	24
23.11 Skin retrieval and processing	25

Chapter 24 Haemopoietic progenitor cells	27
24.1 Terminology	29
24.2 Policy and procedure requirements	29
24.3 Safety requirements	29
24.4 Adverse events and reactions	29
24.5 Donor selection, consent and testing	30
24.6 Collection facilities for HPC-A, HPC-M, HPC-C and TC	31
24.7 Component definitions	32
24.8 Haemopoietic progenitor cell processing standards	34
24.9 Storage of cellular therapy products	35
24.10 Testing of haemopoietic progenitor cell donors and components including therapeutic cells	36
24.11 Labelling, packaging, transportation and temperature controls	38
24.12 Release	43
24.13 Transportation	43
24.14 Thawing and infusion	43
24.15 Disposal of haemopoietic progenitor cells	43
24.16 Records	44
Index	45

Preface to addendum (2007) to the seventh edition

This addendum to the Seventh edition contains revisions of Chapters 21, 22, 23 and 24 that take account of the relevant EU Directives* and resulting UK Regulations.

The advice in these printed Guidelines is believed to represent acceptable practice at the time of printing. It is policy to revise these Guidelines as new developments occur. However, it may not be possible to do so at the time of such change and the Guidelines should therefore be used with due regard to current acceptable practice.

As and when it becomes necessary to make further changes to these guidelines, these will be published on the website www.transfusionguidelines.org.uk. Notifications of such changes are also sent to the management of each of the four UK Blood Services, to the British Association of Tissue Banks, British Society of Blood and Marrow Transplantation, and the Health Protection Agency.

In accordance with the Directives, any changes in donor selection criteria that are necessitated by new information about the epidemiology of infections are also notified to the Medicines and Healthcare products Regulatory Agency (MHRA) and to other institutions with Blood Establishment status.

I wish to thank the members of the Standing Advisory Committees who undertook the task of revising or writing the relevant chapters. In particular we wish to thank Caroline Smith for her painstaking preparation of the material for this publication.

* *Directive 2006/17/EC of 8 February 2006 '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'. OJ, 9.2.2006*

Directive 2006/86/EC of 24 October 2006 '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'. OJ, 25.10.2006

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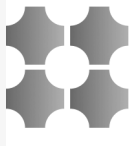
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Tables

Table 22.1	Microbiological testing for tissue donors	8
Table 23.1	Temperature/time relationships for banked tissues	16
Table 23.2	Air classification system for manufacture of sterile medicinal products	17
Table 23.3	Comparison of British, European and American classifications	17
Table 23.4	Microbiological monitoring of controlled work areas	18
Table 23.5	Ethylene oxide and ethylene chlorohydrin residue levels	19
Table 23.6	Minimum donor/recipient data set to be kept	22
Table 24.1	Requirements for the timing of testing	37
Table 24.2	Label content adapted from FACT-JACIE	39
Table 24.3	Label content for HPC-C adapted from NETCORD-FACT	41

Change notification

For the attachment of change notifications as they are issued and notified on www.transfusionguidelines.org.uk.



Chapter 21

Tissue banking: general principles

Regulatory environment in the UK

The whole process of tissue banking is now covered by legislation. The EU Directive 2004/23 (March 2004) has been transposed into UK law. This Directive lays down standards of quality and safety for all aspects of banking of human tissues and cells intended for human applications. In addition the Human Tissue Act 2004 applies throughout the UK with the exception of Scotland, where the Human Tissue (Scotland) Act 2006 applies.

All tissue establishments need to be licensed by the competent Authority which in the case of the UK is the Human Tissue Authority.

Every tissue establishment shall designate a responsible person (Designated Individual) who shall be responsible for ensuring that all activities relating to human tissues and cells intended for human application are in accordance with the laws in force in the UK (Article 17).

It is therefore the responsibility of the Designated Individual to ensure that all the requirements of the HTA are met in a timely and comprehensive manner.

Data protection and confidentiality

Living donors and families of deceased donors must be told that information relating to the donation will be stored in accordance with the Data Protection Act (DPA) 1998 and may be shared with relevant health professionals.

Tissue establishments shall take the necessary measures to ensure that all data, collated within the scope of all their banking activities and to which third parties have access, have been rendered anonymous so that neither donor nor recipients remain identifiable.

Reference documents for tissue banking and haemopoietic progenitor cells

The advice contained in these Guidelines is believed to represent acceptable practice at the time of printing. It is policy to revise these Guidelines as new developments occur. However, it may not be possible to do so at the time of such change and the Guidelines should therefore be used with due regard to current acceptable practice.

The guidelines in this section apply to tissue banking activities within the Blood Transfusion Services of the UK. They must be read in conjunction with the other sections of the guidelines including those that apply to care and selection of blood donors, quality systems, quality assurance and to testing of donors.

Reference should be made to the current version Joint UKBTS/NIBSC Professional Advisory Committee's *Donor Selection Guidelines* available at www.transfusionguidelines.org.uk.

Note should also be made of various UK legal statutes and relevant documents which apply to tissue banking, and documents from the Council of Europe and the European Directives. These include the following:

UK legal statutes and documents relevant to tissue banking

Note: this list is current for 2007.

1. Department of Health. *A Code of Practice for Tissue Banks: Providing Tissues of Human Origin for Therapeutic Purposes*. DoH, February 2001. ISBN 1-84182-329-5.
2. Department of Health. *Decontamination of Medical Devices*. HSC 2000/032, 18 October 2000.
3. Department of Health. *Guidance on the Microbiological Safety of Human Tissues and Organs used in Transplantation*. Advisory Committee on Microbiological Safety of Blood and Tissues for Transplantation, DoH, August 2000. www.advisorybodies.doh.gov.uk/acmbtt.
4. Department of Health. *Variant Creutzfeldt-Jakob Disease (vCJD): Minimising the Risk of Transmission*. HSC 1999/178, 13 August 1999.
5. Department of Health. *Controls Assurance in Infection Control: Decontamination of Medical Devices*. HSC 1999/179, 13 August 1999.
6. Medical Research Council. *Operational and Ethical Guidelines for Collections of Human Tissue and Biological Samples for Use in Research*. Report of the Medical Research Council Working Group, November 1999.
7. Report of the Working Party of the Royal College of Pathologists and the Institute of Biomedical Science. Third Edition (2005) *The Retention and Storage of Pathological Records and Archives*.
8. General Medical Council booklets (available at www.gmc-uk.org):
 - Confidentiality: Protecting and Providing Information*: April 2004
 - Serious Communicable Diseases*: October 1997
 - Good Medical Practice (Third Edition)*: May 2001
 - Seeking Patients' Consent: the Ethical Considerations*: November 1998
 - Research: the Role and Responsibility of Doctors*: February 2002
9. Department of Health, *A Code of Practice for the Diagnosis of Brain Stem Death Including Guidelines for the Identification and Management of Potential Organ and Tissue Donors*. Department of Health, March 1998 available at www.dh.gov.uk.
10. *Transmissible Spongiform Encephalopathy Agents: Safe Working and the Prevention of Infection*. Advisory Committee on Dangerous Pathogens Spongiform Encephalopathy Advisory Committee. June 2003 available at www.dh.gov.uk.
11. *Health Technical Memorandum (HTM) 2010 Sterilization* www.nhsestates.gov.uk.
12. *Health Technical Memorandum (HTM) 2030 Washer-Disinfectors* www.nhsestates.gov.uk.
13. *Health Technical Memorandum (HTM) 2031 Clean Steam for Sterilization* www.nhsestates.gov.uk.

14. *Data Protection Act 1998*, ISBN 0-10-542998-8 available at www.hmso.gov.uk.
15. *The Anatomy Act 1984 (Commencement) Order 1988*, ISBN 0-11-086081-0 available at www.legislation.hmso.gov.uk.
16. Department of Health, The Caldicott Committee, *Report on the Review of Patient-Identifiable Information*. December 1997 available at www.dh.gov.uk.
17. Medicines and Healthcare products Regulatory Agency (2007) *Rules and Guidance for Pharmaceutical Manufacturers and Distributors*, Pharmaceutical Press, ISBN 978-0-85369-719-0.
18. Nuffield Council of Bioethics (1995) *Human Tissues: Ethical and Legal Issues* available at www.nuffieldbioethics.org.
19. *Human Organ Transplants Act 1989 (Scotland)*, ISBN 0-10-543189-3 available at www.opsi.gov.uk.
20. *Human Tissue Act 2004 (except Scotland)*, ISBN 0-10-543004-8 available at www.legislation.opsi.gov.uk.
21. *Human Tissue (Scotland) Act 2006*, ISBN 0-10-590094-X available at www.show.scot.nhs.uk.
22. *Coroners Act 1988*, ISBN 0-10-541388-7 available at www.opsi.gov.uk.
23. Department of Health, HSG (93)40: *Protecting Health Care Workers and Patients from Hepatitis B and Addendum to HSG (93)40* available at www.dh.gov.uk.
24. Department of Health, *Human Bodies, Human Choices the Law on Human Organs and Tissue in England and Wales a Consultation Report*. July 2002 available at www.dh.gov.uk.
25. Department of Health, *Human Bodies, Human Choices: Summary of the Responses to the Consultation Report*. April 2003 available at www.dh.gov.uk.
26. Department of Health, *Saving Lives, Valuing Donors: A Transplant Framework for England*. July 2003 available at www.dh.gov.uk.
27. *Joint UKBTS/NIBSC Professional Advisory Committee's Position Statements "Consent to Tissue Donation"* available at www.transfusionguidelines.org.uk.

Documents from the Council of Europe

28. Council of Europe, *Convention for the Protection of Human Rights and Dignity of the Human Being with Regard to the Application of Biology and Medicine: Convention on Human Rights and Biomedicine*. Oviedo, 4IV. 1997, European Treaty Services/164 www.conventions.coe.int.
29. *Solutions for Organ Preservation*. European Pharmacopoeia, monograph No. 1264 (supplement 5).
30. Council of Europe (2007) *'Guide to safety and quality assurance for the transplantation of organs, tissues and cells, Third Edition'*. ISBN 978-92-871-6037-9 available from Council of Europe publishing at www.coe.int.

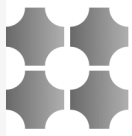
European Union Directives

These are listed in Chapter 1.

31. Directive 2004/23/EC *'on setting standards of quality and safety for the donation, procurement, testing, processing, preservation, storage and distribution of human tissues and cells'*. OJ, L 102, 07.04.2004, p48.
32. Directive 2006/17/EC of 8 February 2006 *'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'*. OJ, 9.2.2006

33. Directive 2006/86/EC of 24 October 2006 *‘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’*. OJ, 25.10.2006

These Directives became legally binding throughout the UK from April 2007.



Chapter 22

Tissue banking: selection of donors

22.1 General considerations

The overall responsibility for applying the policies for the selection and care of tissue donors lies with the tissue bank designated clinician, who must have relevant clinical experience and will be familiar with the various legal statutes and relevant documents which apply to tissue banking. The tissue bank designated clinician must consult with relevant specialist advisors as appropriate.

The designated clinician will rely on procedures and documentation that enable the appropriate medical and behavioural history to be acquired, to prevent microbial infection and transmission of disease (including malignant or neurodegenerative disease) to the recipient. Decisions on donor assessment should be consistent with JPAC *Donor Selection Guidelines*.⁽¹⁾

The designated clinician will be responsible for policies regarding consent and counselling.

Tissues must be procured, transported, processed, stored and distributed according to the requirements stated in these guidelines.

Procedures must be in place to document a complete audit trail from donor to recipient. Tissue banks must ensure that tissues can be traced from the donor to the point of issue. It is the responsibility of the hospital to document the fate of the tissue from its receipt to its use or discard. This will ensure that the audit trail can be followed in both directions. Clinicians caring for the recipients of tissues associated with risks identified following the issue of tissue must be informed where pertinent. Mechanisms should be in place to ensure that confidentiality is maximized.

United Kingdom Blood Transfusion Services Tissue Banks may collect tissues from donors referred to them by a third party such as a Donor Transplant Co-ordinator or another tissue bank and may also refer donors to other tissue banking agencies such as a cornea or research bank. Whenever information regarding donor medical and behavioural history and/or consent for donation is obtained by, or on behalf of a third party this must be subject to a written agreement between the parties involved. The agreement must specify what information is required regarding the medical and behavioural history of the donor and consent for donation, the standards for obtaining this information and the responsibilities of both parties in ensuring that the information is accurate and properly

documented. The information should, as a minimum, be provided in accordance with the guidance in this document and the current JPAC *Donor Selection Guidelines*.⁽¹⁾ It is the responsibility of the designated clinician to determine the bank's policy for the referral of donors.

22.2 Consent

Consent must be obtained and documented by appropriately trained professionals competent in the issues and processes of tissue donation. No coercion or inducement to donate must be applied during the consent procedure. The statutory requirements for consent are detailed in the relevant national legislation, the Human Tissue Act (2004) and the Human Tissue (Scotland) Act 2006. Further detailed guidance is laid out in the Human Tissue Authority 'Code of Practice' on consent (2006).

Living donors must be competent to give consent before donations can be accepted. Consent must cover retrieval, testing (including for HIV), discard and access to medical records. If the tissue may be used for research and development specific consent must be obtained for this as well. Explicit information must be given if tissues are to be retrieved for specific commercial use. Where donors are not competent, national legislation, the guidance of the Nuffield Council of Bioethics (1995) *Human Tissue: ethical and legal issues*⁽²⁾ and the Human Tissue Authority must be followed.

When a deceased person (whilst alive and competent) has explicitly consented to donation of organs and tissues then that consent is sufficient for the activity to be lawful. Where the wishes of the deceased are unknown, the Human Tissue Acts rank persons in a qualifying relationship for the purpose of obtaining consent to organ and tissue donation. The consent of the highest ranking person at the time of death should be sought. In circumstances where this person does not wish to deal with the issue of consent, or is unable to do so, the next person in the ranking order is approached, but it is advisable to record this in the notes. Consent must cover retrieval, testing, storage, discard and access to medical records. If there are circumstances where the tissue may be used for research and development, or teaching, specific consent must be obtained for this as well. Explicit information must be given if tissues are to be retrieved for specific commercial use. For more specific details the UKBTS position statement on 'Consent to Tissue Donation' should be consulted.

Living donors and families of deceased donors must be informed that information relating to the donation will be stored in accordance with the Data Protection Act and may be shared with relevant healthcare professionals.

For deceased donors, information to be supplied to the next of kin regarding various aspects of tissue donation which forms the basis of consent should include the following:

- that reconstruction will be performed following retrieval
- explicit information on which tissue is to be retrieved and the clinical purpose to which it is to be put
- if tissue is found to be unsuitable for clinical transplantation it will be discarded via local discard policies or, if permission is granted, it may be used for research or educational purposes
- that the donor will be tested for markers of microbial infection including HIV and after individual case assessment, those relevant contacts will be informed in the event of a relevant confirmed positive result
- that details of medical and behavioural history will be sought from additional professional sources and recorded.

Where the Coroner (the Procurator Fiscal in Scotland) is in legal possession of the body, permission must be requested to undertake the retrieval.

22.3 Medical and behavioural history

For living donors

Medical and behavioural history must be sought by appropriately trained professionals and in compliance with the following guidance.

- Information must be obtained by face-to-face interview with the donor. This must allow for the exclusion of lifestyle infectious risks. During interviews, a mechanism should be in place to ensure that confidentiality is maximized.
- The interview must be conducted while the donor is free from the effect of anaesthetic, hypnotic, or narcotic medication. The donor must be mentally competent to give an accurate history.
- If the medical interview is not done at the time of admission for surgery, a system must be in place to capture any relevant medical and behavioural history changes that may occur in the interval between interview and donation.
- A standard questionnaire to elicit the medical and behavioural history must be used.
- Donors should be selected according to the JPAC *Donor Selection Guidelines*⁽¹⁾
- The completed questionnaire must be retained as part of the tissue bank donor record.
- The medical records, if available, must be consulted to review the medical and behavioural history and the medical examination.

Further medical history may be sought, where appropriate, from:

- the general practitioner
- any other relevant medical personnel.

For deceased donors

The cause of death and the medical and behavioural history should elicit whether the donor meets the selection criteria outlined in the JPAC *Donor Selection Guidelines*.⁽¹⁾

Modifications for the behavioural and medical history questions may be needed when accepting paediatric donors. Where the deceased donor is less than 18 months of age, or breast fed within the 12-month period prior to donation, the mother's risk for transmissible disease must also be evaluated. Information must be sought from the following sources by appropriately trained professionals and must be documented using a standard form:

- the donor's next of kin or other person identified as the most likely to be in possession of relevant information
- the medical notes if the donor was admitted to hospital prior to death
- the general practitioner
- the post-mortem (where one is undertaken). If no post-mortem is undertaken, the cause of death of the donor, as ascertained from the medical notes, must be documented in the tissue bank donor record.

A record must be made of how the donor was identified, e.g. toe tag, wristband, etc.

The deceased donor's external appearance should be thoroughly examined at the time of retrieval. The appearance must be documented with respect to the donor's medical and behavioural history, including the presence of any obvious medical intervention, scars, tattoos, skin or mucosal lesions, jaundice, infection, trauma, or needle tracks.

A note should be made of when the donor's death was recorded and by whom. The estimated time of death must be documented.

All the above information for living and deceased donors should be reviewed by the designated clinician who is familiar with the relevant standards in the field of tissue banking (see Chapter 21).

22.4 Tissue-specific donor considerations

Reference must be made to the JPAC *Donor Selection Guidelines*⁽¹⁾ document for ages and other specific donor requirements for different tissues.

22.5 Donor testing

The general principles of microbiological testing that apply to living blood donors (see Chapter 10) will also apply to the testing of tissue donors. In particular, assays should be validated, approved by United Kingdom Blood Transfusion Services as fit for purpose and compliant with Directive 98/79/EC on ‘*in vitro* diagnostic medical devices’.⁽³⁾ When assays have been validated for post-mortem blood samples and have been evaluated and approved by the United Kingdom Blood Transfusion Services, such assays must exclusively be used if no ante-mortem sample is available. Mandatory testing must only be undertaken by Clinical Pathology Accreditation (CPA) accredited laboratories or in Medicines and Healthcare Products Regulatory Agency (MHRA) licensed laboratories. If a third-party laboratory is used to perform any aspect of donor testing, the specific requirements and responsibilities of both parties in achieving them must be defined in a written agreement. Such testing should, as a minimum, be performed in accordance with the guidance in this document. There should be protocols for assuring the veracity and security of the sample, labelling, and supporting documentation. The time from sample acquisition to testing or freezing of the sample should be minimized and must be consistent with test kit manufacturers’ recommendations or validated for the purpose. Due consideration should be given to dilution of the sample (see Section 22.7).

All tissue donors (deceased or living) should be tested to the same minimum standards as required for blood donors. In addition further testing is required depending on both the type of donor and the timing of the blood sample relative to donation (see Table 22. 1). All tissue donors now require an anti-HBc test. For deceased donors single sample (rather than pooled) anti-HTLV and NAT testing is required. For living donors either additional NAT testing on the donation sample or a second post-quarantine blood sample are required. Note that a non-pooled sample must be used whenever testing is required for HBV-DNA (see Table 22. 1).

Table 22.1 Microbiological testing for tissue donors

donor type	sample	microbiological testing requirements for blood samples																		
		donation sample										post-quarantine sample								
		sypilis	HBsAg	anti-HCV	anti-HIV	anti-HTLV pooled	HCV-PCR pooled	anti-HBc	HIV-PCR pooled	HBV-PCR single	anti-HTLV single	HCV-PCR single	HIV-PCR single	sypilis	HBsAg	anti-HCV	anti-HIV	anti-HTLV pooled	HCV-PCR pooled	anti-HBc
living donor																				
surgical bone donor	single																			
amniion donor (maternal sample)	single	Y	Y	Y	Y	Y	Y	Y	Y	Y										
	two samples	Y	Y	Y	Y	Y		Y						Y	Y	Y	Y	Y		Y
dead donor																				
deceased donor		Y	Y	Y	Y	-	-	Y	-	Y	Y	Y	Y							
deceased infant donor	infant sample	Y	Y	Y	Y	-	-	Y	-	Y	Y	Y	Y							
	maternal sample	Y	Y	Y	Y	Y	Y	Y	Y	Y										

The tissue bank should have a documented policy to follow in the case of live or deceased donors, with repeat reactive screening tests (see Chapter 10). There should be protocols for retesting, if appropriate, confirmatory testing, counselling of donors and contacts and acceptance or rejection of donations. Reports of positive tests should be included in the routine donor surveillance programmes and notified to the appropriate statutory authority.

Rh D testing may be required on donors if the retrieved tissues will contain residual red cells or red cell membranes at the time of implantation.

22.6 Testing of living donors

All blood samples from living donors must be acquired using positive donor identification by an individual trained to ensure the security of the sample and supporting documentation.

Living donors can be tested by **either** a single sample taken at the time of donation where testing includes a nucleic acid amplification technique (NAT) for HIV, HBV and HCV **or** by two samples including a post-quarantine sample where additional NAT testing is not required.

Where only a single sample is tested the ‘donation sample’ must be obtained at the time of donation or, if not possible, within seven days post-donation.

Where two samples are tested the ‘post quarantine sample’ is required after an interval of at least 180 days from the date of donation. In these circumstances of repeat testing, the donation sample can be taken up to 30 days prior to and 7 days post donation. When the donation blood sample is taken prior to the date of tissue donation a system must be in place to ensure that the pre-quarantine sample reflects the risk status at the time of donation.

For amnion donation, only a maternal sample requires to be tested for mandatory markers of infection (not a cord blood sample).

22.7 Testing of deceased donors

Appropriate mechanisms must be in place to ensure:

- the secure identification of samples obtained from hospital laboratories
- where there is doubt about the identity of a blood sample from a tissue donor (inadequate labelling), DNA profiling may be accepted as an accurate method for confirming the identity of the blood sample
- documentation of the date the sample was taken, the name of the individual and laboratory supplying the sample and sample storage conditions.

An ante-mortem blood sample, up to seven days preceding death, is always preferable to a post-mortem sample for testing. Where no ante-mortem sample is available, then a post-mortem sample can be used. Samples for testing must not be taken more than 24 hours post-mortem and the time from sampling to testing or freezing of the sample should be minimized and must be consistent with test kit manufacturers’ recommendations or validated for the purpose.

The anatomical site from which the postmortem sample was obtained and the time of sampling must be documented. The sample appearance should be documented. If the sample appears dilute or grossly haemolyzed, a repeat sample preferably from an alternative site should be obtained if possible. Tissue banks should have a protocol for post-mortem sampling, clearly defining preferred sites for sampling, e.g. cardiac puncture or femoral vessel puncture and avoiding sites close to intravenous lines.

Where a deceased donor has received ante-mortem transfusions, a pre-transfusion sample should be used whenever possible for testing. If a pre-transfusion sample is not available, tissue banks must employ an algorithm incorporating the timing, nature and volume of the fluids infused and the donor’s own blood volume as well as any blood loss from the

intravascular space, to assess any resultant plasma dilution (see JPAC *Donor Selection Guidelines*⁽¹⁾ for an example of a deceased donor intravenous fluid report form). Samples of blood estimated to be more than 50% dilute are not suitable for testing.

Samples relating to deceased donors must be subject to single sample (not pooled) for the following:

- HIV-RNA
- HCV-RNA
- HBV-DNA
- anti-HTLV

This applies to both ante-mortem and post-mortem samples. NAT tests used on post-mortem samples must be validated for such use, in particular to ensure that any impact of inhibitors is eliminated.

Screening and confirmatory tests must be performed as specified in Chapter 10. In the case of repeatably reactive screening tests confirmatory testing is required for counselling purposes.

Repeatably reactive screening tests from post-mortem samples will debar tissues from release unless a superior sample can be obtained, e.g. obtained ante-mortem or closer to the time of death, and this sample is tested and negative results are obtained from a designated diagnostic laboratory. The acquisition of the 'superior' sample must be subject to the same requirements given above.

Where the deceased donor is less than 18 months of age a maternal sample must be tested as well as an infant sample. Maternal samples are also required in the case of older children who have been breast fed within the 12-month period prior to donation. The maternal sample will be tested as for a living donor whilst the infant's sample should be tested as for a deceased donor (see Table 22.1).

22.8 Follow up

Follow up must be provided (where deemed appropriate) for living donors who, on confirmatory testing, have positive or indeterminate results. In these cases appropriate referral for further medical follow up and assessment must be ensured. Confidentiality must be ensured and the donor's permission sought prior to the counselling of relevant contacts.

For deceased donors individual cases must be assessed by the designated clinician with relevant advice. Relevant contacts of deceased donors with confirmed positive test results should be confidentially informed of such results if relevant to their health. Appropriate specialist referral should be offered.

22.9 Autologous tissue donation

The designated clinician should decide the policy in relation to the provision of an autologous service.

Autologous donors should be tested for the same mandatory microbiological markers as for an allogeneic living donor. Microbiological testing must include bacteriological culture where tissue does not undergo a validated terminal antimicrobial treatment. The medical history may be less relevant than for allogeneic donation of tissues. The rationale for any exceptions must be documented.

Separate storage must be used to avoid inappropriate issue. Autologous tissue must be securely segregated from allogeneic tissue at all stages from collection to issue. Autologous donations may not be transferred to the allogeneic bank.

A system must be in place to enable the hospital to recognize that the tissue is autologous. The autologous tissue must be labelled with the donor/recipient name, hospital number and date of birth.

22.10 Archiving of donor samples

An archive blood sample should be kept for look-back investigations in the event of an adverse reaction. This must be for a minimum of 11 years after the expiry date of the tissue with the longest storage life.

Tissues can be held for a number of years prior to issue eg bone (3 years) and heart valves (10 years). During this period in storage there may be changes to the mandatory microbiology test requirements and improvements in screening assays for mandatory or other markers. Consideration should be given for an additional blood sample archive for tissues with a long expiry for possible future testing that is not currently available.

A policy regarding the need for re-testing of the tissue inventory needs to be established. Any policy adopted must be operationally feasible and will depend on both the maximum storage period of the tissue and the probability of the tissue being issued. When new, or significantly improved, mandatory tests are introduced consideration should be given to the re-testing of archive samples from the donors of tissue still in issuable stock. Where there is no archive sample available to test, a risk assessment must be performed. It should include factors such as the seriousness of the infection, any viral inactivation procedures performed on the tissue, the effect on inventory of discarding such tissues and the severity of impact of possible tissue shortages on recipients.

22.11 Release criteria

For allogeneic donors the results of all screening tests, with the exception of syphilis and anti-HBc, must be negative for a tissue to be released from quarantine for issue. Donors with a positive anti-HBc may be considered as eligible provided an anti-HBs has been documented at more than 100 iu/l at some time.

In the case of a deceased infant donor where a maternal sample is found to be positive for any mandatory marker of infection, the donation must not be used irrespective of the test result for the infant.

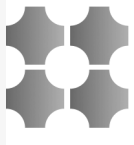
Donors with reactive screening tests for the presence of treponemal infection should be fully assessed, taking into account the results of confirmatory (reference) testing and medical history. Allogeneic donors are considered to be eligible if their screening test results are reactive but confirmatory tests are negative. However the presence of current (active) infection will exclude the use of tissues from such donors. Where the assessment leads to the conclusion that the risk of active infection is remote, then non cardiovascular tissues may be used.

The presence of serological marker patterns of treponemal infections (e.g. IgM positivity) should not be used as a sole criterion to determine the presence of active infection (and therefore their eligibility). The results of confirmatory testing are only part of the assessment process. Any reactive results obtained on confirmatory testing should be discussed with staff experienced in interpreting treponemal test results, before a decision is made to use tissues.

For autologous donors positive test results will not necessarily prevent the tissues or cells or any product derived from them being stored, processed and reimplanted, if appropriate isolated storage facilities are available to ensure no risk of cross contamination with other grafts and/or no risk of mix-ups at issue.

References

1. Joint UKBTS/NIBSC Professional Advisory Committee's (JPAC) *Donor Selection Guidelines* available at www.transfusionguidelines.org.uk.
2. Nuffield Council of Bioethics (1995) *Human Tissue: ethical and legal issues* available at www.nuffieldbioethics.org.
3. Directive 98/79/EC of the European Parliament and of the Council 27th October 1998 on '*in vitro* diagnostic medical devices'. OJ, L331, 07.12.98, p1.



Chapter 23

Tissue banking: tissue retrieval and processing

23.1 General considerations

Tissue banks should have dedicated processing and storage facilities designed and operated to prevent contamination, cross-contamination, mislabelling and deterioration of tissues.

All processes and equipment which affect the safety or quality of tissues must be validated. Tissue bank non-disposable instruments and other items which come into direct contact with donor tissue during retrieval and processing must be thoroughly washed and sterilised between uses. Where possible, disposable equipment should be used. Where this is impractical or impossible, non-disposable instruments can be used. These must be batch-dedicated to allow tracking through decontamination, sterilization and use. A risk assessment should be performed to determine the period for which instruments are kept before discard. These instruments should be washed and sterilised according to NHS Estates Health Technical Memoranda (HTM) 2010,⁽¹⁾ 2030⁽²⁾ and 2031.⁽³⁾ Prompt removal of residual blood and tissues is an important aspect of decontamination, particularly with regard to CJD.

All purchased materials and solutions which affect the tissue quality and safety must be inspected on receipt to ensure compliance with specification. Local policies must be in place to minimize the risk of tissue contamination by staff e.g. by blood from a cut during retrieval and processing.

UK Blood Transfusion Services tissue banks may use third parties to perform tissue retrieval, processing steps such as irradiation, tissue evaluation such as bacterial tests, quality control tasks such as environmental monitoring or tissue storage, transport and distribution. Wherever such tasks are performed by or on behalf of a third party, this must be subject to a written agreement between the parties involved. This must specify the processes to be performed, the applicable standards and specifications and the responsibilities of both parties in achieving the desired outcome. The processes should be performed, as a minimum, in accordance with the guidance given in the EU Directive and its daughter directives.

In the event of a health care worker sustaining an injury such that his/her blood comes into contact with the tissue, the tissue must be discarded.

23.2 Retrieval

Retrieval times and preliminary storage

Tissues should be retrieved as soon after death as possible. If the body has not been refrigerated, procurement of tissues should be completed within 12 hours after death. If the body has been refrigerated within six hours of death, procurement should preferably start within 24 hours and must be completed within 48 hours of death.

Tissues must be placed at a temperature of 0–10°C within four hours of retrieval.

General considerations for tissue retrieval

Every effort must be made to minimize contamination of tissue during procurement.

The procurement facility must be suitable for procurement of tissues, which may include facilities other than an operating room.

A local sterile field must be created using sterile drapes. An appropriate anti-bacterial skin preparation agent must be used before commencing the retrieval.

All instruments used during the retrieval must be sterile and should be stored on a back table which is covered with a sterile drape. Where possible, disposable equipment should be used.

Staff conducting the retrieval must be appropriately gowned in sterile clothing, and wear sterile gloves and protective masks.

Every effort should be made to minimize the number of people present during deceased tissue retrieval and to ensure that a post-mortem is not proceeding during the retrieval.

Where possible the retrieval should precede any post mortem examination of the donor. In cases referred to the Coroner (or the Procurator Fiscal in Scotland), the Coroner's consent must be obtained to enable the retrieval of tissues.

Deceased reconstruction

It is integral to the maintenance of the dignity of the donor that the body is cleaned and reconstruction is carefully undertaken. Whenever long bones are removed they must be replaced with appropriate prostheses. All incisions should be neatly sutured.

For similar reasons, skin must not be procured from the neck, arms, face or other areas that may affect funeral viewing.

Every effort should be made to ensure that appropriate advice on the handling of deceased donors after retrieval should be made available for mortuary and funeral home staff.

Labelling of collections

At the time of collection, the container for each category of tissue, for example skin, bone, or heart valves, must be labelled with the nature of the contained tissue and a barcoded tissue or donor identification (ID) label as appropriate.

The accompanying donation record must be labelled with the same tissue or donor identification number(s), key donor identifiers (name, date of birth, etc.), and the date of collection prior to removal from the procurement site. Bacteriology and blood samples, together with accompanying documentation where relevant, must be labelled according to agreed local procedures such that the results can be linked to the correct donor/tissue whilst still preserving anonymity where required. Annex 4 of the first daughter directive describes (in 1.6) the minimum requirements.

A double container system is required for all tissues retrieved. The containers must not be opened until ready for use or further aseptic processing at a facility approved by the tissue bank.

23.3 Transportation conditions

For viable tissue the grafts should be placed into a transport solution with due regard to its effects on the ability of cells to propagate or metabolise. There must be adequate control of buffering capacity, osmolarity, tissue oxygenation. External contamination and desiccation must be avoided. The type, lot, manufacturer and the expiry date of the transport solution shall be documented. Transportation systems must be validated to show maintenance of the required storage temperature.

23.4 Bacteriostasis and disinfection

Tissue without terminal antimicrobial processing

Tissue must be subjected to one of the following treatments, as soon as possible, within 24 hours of retrieval:

- antibiotic disinfection
- an alternative disinfection method
- deep-frozen storage at -20°C or lower.

In the case of tissue taken from heart-beating donors in the operating theatre at the time of organ retrieval, this period may be extended to 48 hours.

Tissue with terminal antimicrobial processing

Bone from living donors which is refrigerated within four hours of retrieval but not frozen until 24–48 hours after retrieval must be subjected to terminal antimicrobial processing.

Tissue with terminal antimicrobial processing must be subjected to one of the treatments detailed in the above section within 24 hours of retrieval with a maximum of 72 hours following death. A summary of the guidance regarding temperature/time relationships contained in these guidelines is given in Table 23.1.

Positive bacteriology or mycology

It is the responsibility of the designated medical officer or designated microbiologist to develop written policies regarding the selection and conduct of tests for bacterial and fungal contamination and the acceptance criteria for specific tissues.

Where tissues are shown to carry viable bacteria or fungi they may be suitable for clinical use (e.g. skin grafts) depending on microbial types and densities of growth on culture. For other tissues the material may be approved for use providing a validated antimicrobial processing technique is used.

23.5 General guidelines for tissue processing

Processing must not change the physical properties of the tissue so as to make them unacceptable for clinical use. Processing steps must be validated to demonstrate that the final product does not have any clinically significant residual toxicity.

Aseptic processing facilities

Facilities for aseptic processing must comply with the *Rules and Guidance for Pharmaceutical Manufacturers and Distributors 2007*.⁽⁴⁾ They must provide separate work areas with defined physical and microbiological parameters. Facilities must have:

- floors, walls and ceilings of non-porous smooth surfaces that are easily sanitized
- temperature control
- air filtered through high-efficiency particulate air (HEPA) filters with appropriate pressure differential between zones, which must be documented
- a documented system for monitoring temperature, air supply conditions, particle numbers and bacterial colony forming units (environmental monitoring)

Table 23.1 Temperature/time relationships for banked tissues

Retrieval	<p>If the body has not been refrigerated, procurement of tissues should be completed within 12 hours after death.</p> <p>If the body has been refrigerated within six hours of death procurement should preferably start within 24 hours and must be completed within 48 hours of death.</p>
Retrieved tissue	<p>Must be placed at an ambient temperature of 0–10°C within 4 hours of retrieval.</p>
Bacteriostasis	<p>Freezing tissue to at least –20°C within 24 hours of retrieval (or up to a maximum of 72 hours of death) can be used as a bacteriostatic treatment.</p> <p>Bone from living donors which is not frozen until 24–48 hours after retrieval must be subjected to terminal antimicrobial processing.</p>
Long-term storage	<p><i>Frozen tissue</i> may be stored</p> <ol style="list-style-type: none"> 1. At –20°C or lower for up to six months. 2. At –40°C or lower for up to three years. Temporary storage of frozen musculoskeletal tissue between –20°C and –40°C is limited to six months in total. Grafts stored at this temperature must then be transferred to –40°C or colder to give an expiry of up to a maximum of three years from donation. <p><i>Cryopreserved tissue</i> should be stored</p> <ol style="list-style-type: none"> 1. At –135°C or lower to claim a 10-year expiry for all grafts to maintain a reasonable inventory of size matched grafts (e.g. heart valves and menisci). Other cryopreserved tissues should have a three year expiry. 2. At higher temperatures up to –80°C; the same expiry pertains providing it has been validated. <p><i>Glycerol preserved tissue</i></p> <ol style="list-style-type: none"> 1. Skin preserved in high concentration (>90%) glycerol may be stored at 0–10°C for up to two years. 2. Amnion preserved in low concentration (50%) glycerol may be stored below –40°C for up to two years.
Transportation and local storage	<p><i>Frozen tissues</i> must be transported and stored locally prior to clinical use, at –20°C or lower in order to have the designated expiry (specified above).</p> <p><i>Cryopreserved tissues</i> may be transported in the vapour phase of liquid nitrogen (<–135°C) or on dry ice (–79°C). If tissues are transported on dry ice they should continue to be stored locally at circa –80°C until expiry.</p>

- a documented system for cleaning and disinfecting rooms and equipment
- a documented system for gowning and laundry
- adequate space for staff and storage of sterile garments
- access limited to authorized personnel
- documented system for general staff hygiene practices.

Tissue not destined for terminal microbial processing

Critical work areas are those where tissue is manipulated openly either following a disinfection or sterilisation step or in those cases where tissue has been procured aseptically and will not be further disinfected or sterilised. Critical work areas on which sterile containers, aseptically procured tissue or disinfected tissue is exposed to the environment, must have an air quality of grade A and should have a grade B background (see table 23.2 and table 23.4). Any lowering to this standard in the background environment (as long as it is compliant with EU requirements) must be documented and demonstrated that the chosen environment achieves the quality and safety required, at least taking into account the intended purpose, mode of application and immune status of the recipient.

Table 23.2 Air classification system for manufacture of sterile medicinal products

Grade	Max. permitted number of particles per m ³ :			
	At rest		In operation	
	0.5 µm	5 µm	0.5 µm	5 µm
A	3,500	1(b)	3,500	1(b)
B(a)	3,500	1(b)	350,000	2,000
C(a)	350,000	2,000	3,500,000	20,000
D(a)	3,500,000	20,000	Not defined	Not defined

(a) In order to reach the B C and D air grades, the number of air exchanges should be related to room size and the equipment and personnel present in the room.

(b) These areas are expected to be completely free from particles of size greater than or equal to 5 µm

Rules and Guidance for Pharmaceutical Manufacturers and Distributors 2007⁽⁴⁾ and the EC Guide to Good Manufacturing Practice 2003⁽⁵⁾

Table 23.3 Comparison of British, European and American classifications

EC 'Orange Guide' Grade	BS 5295	ISO 14644	US 209D 1989 Class
A, B	F	5	100
C	J	7	10,000
D	K	8	100,000
–	L	–	–

Table 23.4 Microbiological monitoring of controlled work areas

Grade	Air sample cfu/m ³	Settle plates (diam. 90mm) cfu/4hrs	Contact plates (diam. 55mm) cfu/plate	Glove print 5 finger cfu/glove
A	<1	<1	<1	<1
B	10	5	5	5
C	100	50	25	–
D	200	100	50	–

Rules and Guidance for Pharmaceutical Manufacturers and Distributors 2007.⁽⁴⁾

Wherever possible, representative samples of tissue should be removed and tested for bacterial and fungal contamination using protocols authorised by the designated medical officer or designated microbiologist. Swabs or other validated non-destructive sampling methods should be used where it is impossible to remove tissue without damaging the graft. Microbiological inclusion/exclusion criteria should be developed by the designated medical officer or designated microbiologist in accordance with national policy.

Where tissues are processed in batches, procedures must ensure that no cross-contamination between batches can occur. Key process parameters and acceptance limits must be identified and validated. A full record of each process applied to each tissue or batch must be filed in the pool record.

Tissue destined for terminal microbial processing

Work areas in which tissue materials and containers are prepared should have an environment with air quality of at least Grade C (Class 10,000), or better, in the vicinity of exposed tissue.

Terminal anti-microbial processing must follow the filling of the final container. The procurement, processing and filling environment must be of sufficient quality to minimize the microbial contamination of the tissue to ensure that the subsequent antimicrobial processing is effective.

The tissue in its final container must be subjected to a validated procedure utilising an agent such as gamma irradiation or ethylene oxide gas. Ethylene oxide should be avoided unless there is no alternative that provides the required properties for clinical effectiveness. The processing method and dose of the sterilant should be validated as sufficient to bring about at least a six logarithms reduction in a recognised marker resistant organism e.g. *Clostridium sp.* for irradiation.

Physical or chemical indicators must be used according to manufacturer's instructions with each batch to document exposure to the sterilant, either ethylene oxide or gamma irradiation.

Gamma irradiation

Gamma irradiation must be performed in a controlled manner to ensure that all tissue receives at least the minimum specified dose of radiation. This requires the use of standard packaging materials and irradiator load configuration and is usually validated using calibrated dosimeters placed throughout the load. The dose should never be less than 15 KGy, unless pre-irradiation processing has been validated to consistently yield a low microbial bioburden such that there is the required assurance, in accordance with medical device standards, that the dose will result in the tissue being sterile.

Tissue must be irradiated in its final packaging, which must bear a suitable indicator to demonstrate that it has been irradiated. This must be checked before release of the tissue.

If a dose in excess of 25 KGy is required, then consideration must be given to the possible detrimental effect on the biological and physical properties of the tissue.

Many viruses are resistant to irradiation and therefore any claim of viral inactivation must be supported by validation data obtained using appropriate marker viruses.

Ethylene oxide

Ethylene oxide anti-microbial processing procedures must assure the maintenance of the manufacturer's recommended humidity, temperature and ethylene oxide concentration.

A biological spore test indicator (*Bacillus niger* var. *subtilis*) must be included in each ethylene oxide batch and used and interpreted according to the manufacturer's instructions.

Each type of tissue must be tested for ethylene oxide and ethylene chlorohydrin residues. The testing must be repeated each time the process is changed. The residue levels must not exceed the suggested maximum acceptable residue levels as listed in Table 23.5.

Table 23.5 Ethylene oxide and ethylene chlorohydrin residue levels
(Residuals parts per million)

Medical device implant	Ethylene oxide (ppm)	Ethylene chlorohydrin (ppm)
Small (< 10 g)	250	250
Medium (10–100 g)	100	100
Large (> 100 g)	25	25

Pooling

Pooling of tissues from different donors is not permitted.

Preservation methods

Where specific attributes of a tissue are claimed the process should be validated to show these attributes are preserved.

Freeze-drying

Where tissues are freeze-dried, a sample of each type of tissue from each freeze-drying run must be analysed for residual moisture content which must be less than 5% (weight/weight) of the dry weight of the graft to allow a three-year expiry at ambient temperature.

Glycerolization

Where tissues are preserved by high concentrations of glycerol the procedure should be validated to demonstrate achievement of the specified glycerol concentration within the tissue or acceptable range within the tissue.

Cryopreservation

Cryopreserved tissue must be stored below -135°C to allow a 10-year expiry for size matched grafts and three-year expiry for other tissues. For storage at higher temperatures, validation must be performed to demonstrate that the required properties of the graft are maintained for the stated expiry.

Solutions

Rinse solutions, antibiotic mixtures, nutrient media and cryopreservation solutions must be stored at a specified temperature and with a storage period consistent with functional requirements. They must be discarded if not used within 24 hours of opening. Any solutions coming into direct contact with tissues during retrieval or processing must be sterile.

23.6 Tissue storage

Refrigeration devices containing tissue shall be suitable for the use intended and procedures for monitoring such devices shall be validated so that tissues are maintained at the required storage temperature. Continuous monitoring and recording of temperature,

together with suitable alarm systems, shall be employed on all storage refrigerators, freezers and liquid nitrogen tanks.

Every effort should be made to avoid cross-contamination of material stored in liquid nitrogen vessels. Wherever possible there should be specifically designated pieces of equipment (e.g. nitrogen level rulers, portable thermometers) for each vessel. Where this is not possible (e.g. liquid nitrogen delivery hoses) and the item has to be used for more than one vessel, it should not come into contact with the liquid phase or the sides of the vessel.

Frozen tissue should be double wrapped during storage. The seals and the material employed must be validated for their use at the designated storage temperature and the conditions of use, to demonstrate integrity of the packaging and labelling. This is crucially important for storage with liquid nitrogen owing to the high levels of accumulated microbial contaminants in liquid nitrogen storage vessels.

Quarantined and released tissue must be stored in physically segregated, clearly designated locations distinct from each other.

Tissue release

Prior to any tissue being cleared for issue, all relevant records including donor records, processing and storage records, and post-processing quality control test results must have been reviewed, approved and documented as acceptable by the individual(s) responsible according to the relevant local SOPs. Responsibilities for setting policies for exceptional release of tissues resides with the designated medical officer.

Tissue discard

There must be a documented policy for the discard of tissue unsuitable for clinical use. Records should include details of date and method of discard and reason for discard. Tissues for discard should be appropriately handled and disposed of in a manner compliant with local control of infection guidelines.

Labelling and packaging of tissues for issue

Packaging must ensure integrity and maintain sterility of the contents of the final container, and must also comply with current legislation.

The container must be labelled with the graft-specific identification (batch and shipment number if applicable), expiry date and supplying tissue bank, storage instructions and barcoded product description and instruction to see pack insert, as a minimum. In addition, more detailed information should be provided either on the label or package insert or both as follows:

- sizing information
- anti-microbial processing procedure used (if applicable)
- preservative used and its concentration (if applicable)
- special instructions (e.g. 'Do not freeze'), thawing, dilution instructions
- presence of known sensitizing substances
- type and calculated quantity of antibiotics added during processing (if applicable)
- any other potential residual processing agent
- Rh D type (where appropriate)
- a statement that the tissue was prepared from a donor who was non-reactive for current mandatory markers of infection, with the added rider that all biological tissue carries some risk of disease transmission
- results and findings from clinically relevant bacteriological cultures performed on the tissue before final packaging

- storage instructions
- instructions for reconstitution (if appropriate)
- a warning on loss of package integrity
- instructions on dealing with queries, reporting adverse events/reactions and return or disposal of unsuitable or unused tissue
- a statement that tissue use must be authorised by a medical/dental practitioner
- a statement should accompany each tissue product stating that it may not be sterilized after leaving the tissue bank
- a statement should accompany each package stipulating that each package is for single-patient use only
- if the package insert carries graft-specific information it must be labelled with the unique graft-specific identification code
- instructions to the user regarding the need for a documented system for the tracking and follow-up of the fate of the tissue
- when cells are known to be positive for a relevant infectious disease marker, it must be marked as a BIOLOGICAL HAZARD.

External labelling of the shipping container

For transport, the primary container must be placed in a shipping container that must be labelled with at least the following information:

- (a) identification of the originating tissue establishment, including an address and phone number;
- (b) identification of the organisation responsible for human application of destination, including address and phone number;
- (c) a statement that the package contains human tissue/cells and HANDLE WITH CARE;
- (d) where living cells are required for the function of the graft, such as stem cells gametes and embryos, the following must be added: 'DO NOT IRRADIATE';
- (e) recommended transport conditions (e.g. keep cold, in upright position, etc);
- (f) safety instructions/method of cooling (when applicable).

Distribution

All reasonable efforts must be made to ensure that tissues are sent to qualified individuals/organizations who have accepted responsibility for their proper handling and use.

Where tissue is transported in a refrigerated or frozen condition, adequate safeguards should be taken to ensure that the tissue remains at the designated temperature.

Monitoring of temperature should be undertaken wherever practicable but if not, the method should at least have been validated to show that appropriate temperatures are maintained.

23.7 Tracking of tissues

Each Tissue establishment shall ensure that it has the ability to locate and identify all tissues/cells during any step from procurement through to distribution to recipient or disposal and vice versa. This traceability shall also apply to all relevant data relating to products and materials coming into contact with these tissues and cells.

Tissue establishments shall have effective and accurate systems to uniquely identify and label tissues/cells received and distributed.

Tissue establishments shall keep the data necessary to ensure traceability at all stages. Data required for full traceability shall be kept for a minimum of 30 years after clinical use. Data storage may also be in electronic form. Data that must be kept are shown in Table 23.6 (Annex VI, Directive 2006/86/EC of 24 October 2006).

Table 23.6 Minimum donor/recipient data set to be kept

A. BY TISSUE ESTABLISHMENTS

Donation identification that will include at least:

- Identification of the procurement organisation or tissue establishment
- Unique Donation ID number
- Date of procurement
- Place of procurement
- Type of donation (e.g. single v multi-tissue; autologous v allogenic; living v deceased)

Product identification that will include at least:

- Identification of the tissue establishment
- Type of tissue and cell/product (basic nomenclature)
- Pool number (if applicable)
- Split number (if applicable)
- Expiry date
- Tissue/cell status (i.e. quarantined, suitable for use etc.)
- Description and origin of the products, processing steps applied, materials and additives coming into contact with tissues and cells and having an effect on their quality and/or safety
- Identification of the facility issuing the final label

Human application identification that will include at least:

- Date of distribution/disposal
- Identification of the clinician or end user/facility.

B. BY ORGANISATIONS RESPONSIBLE FOR HUMAN APPLICATION

- (a) Identification of the supplier tissue establishment
 - (b) Identification of the clinician or end user/facility
 - (c) Type of tissues and cells
 - (d) Product identification
 - (e) Identification of the recipient
 - (f) Date of application
-

23.8 Notification of serious adverse events and reactions

Tissue establishments shall ensure that there is a system in place to report, investigate, register and transmit information about serious adverse events and reactions which may influence the quality and safety of tissues and cells, which may be attributable to the procurement, testing, processing, storage and distribution of tissues and cells as well as any serious adverse reactions observed during or after clinical applications which may be linked to the quality and safety of tissues and cells.

All persons and tissue establishments using human tissues and cells regulated by this Directive shall report any relevant information to tissue establishments to facilitate traceability and assure quality and safety control.

The tissue establishment shall ensure that the HTA is notified of any serious adverse events and reactions according to procedures laid down by the authority. A root cause analysis should be performed. Moreover each tissue establishment shall ensure that an accurate, rapid and verifiable procedure is in place which will enable it to recall from distribution any product which may be related to an adverse event or reaction.

23.9 Additional guidelines for skeletal tissue retrieval and processing

Procurement of surgically removed bone

A system of documentation must be in place to ensure that theatre staff are clearly informed that a particular patient has or has not consented to bone donation. This may be by enclosing a copy of the consent form in the patient's notes, or some equivalent method.

Where bones are retrieved during surgery by theatre staff on behalf of the tissue bank, these staff must follow a protocol provided by the tissue bank in accordance with third party agreements.

The removed bone should be placed, as quickly as possible, in a sterile container and labelled in a manner to distinguish it from cleared issued bone.

If the donated bone is not destined for terminal antimicrobial processing, it must be cultured for microbial contamination at the time of collection, using a collection and transport system provided by, or approved by, the tissue bank. Bone sampling must be carried out immediately prior to closing the bone container.

Tissue samples for culture should comprise of chips of bone from the cut end of the bone, which should be placed in appropriate transport or culture media. The bone should be finally packaged in a double sterile container.

The bone container, tissue samples and blood samples, if collected at this time, must be clearly labelled with the barcoded donation number and stored cool until collection.

A secure system utilizing barcodes for the identification and linkage of the donation to the donor and samples must be in place.

Documentation must be completed in theatre, detailing the time of bone retrieval and providing the identity of the staff members carrying out the retrieval and labelling.

Alternatively protocols can be put in place to arrange for the hospital blood bank or other appropriate laboratory, to separate serum from the blood samples and to store it and the donation at -20°C or lower, for collection at a later date. Testing should be performed within one month of sampling.

Bone which is not subject to antimicrobial processing can only be released for use if cultures for aerobic and anaerobic bacteria, and fungi are negative.

Where environmental contaminants are detected on surgically retrieved bone, this bone may be further processed and exposed to either gamma irradiation (> 1.5 megarads = $> 15\text{KGy}$) or ethylene oxide (see Section 23.5).

Procurement of skeletal tissues from cadavers

If iliac crest is to be retrieved, it should be taken last in case the bowel is perforated and stored in a separate container. Where osteochondral allografts are to be retrieved, care should be taken to avoid drying of articular surfaces. It is best to retrieve the joint entirely and to dissect it later in the laboratory.

Processing of skeletal tissues

Cycles of thawing and freezing must be minimized. Skeletal tissues should not be heated above 60°C and tendons and costal cartilage should not be warmed above 30°C .

The maximum storage period for frozen skeletal tissues depends upon the degree of prior processing and the storage temperature. Frozen bone should be stored at temperatures of -40°C or colder with the exception of short term storage (less than six months), which can be at -20°C or lower. Storage at -40°C or lower for up to three years is accepted current practice (see Table 23.1).

Osteochondral allografts, such as proximal or distal femur or femoral hemicondyles, are frozen with cryoprotectant (such as DMSO) on the articular surfaces and cooled following appropriate cryopreservation protocols. Cryopreservation of allografts must begin within

48 hours of procurement. These allografts must not be exposed to ethylene oxide or gamma irradiation and must therefore be procured and processed aseptically.

23.10 Cardiovascular tissue retrieval and processing

General

This section predominantly relates to the banking of heart valves.

Sizing and evaluation of cardiovascular tissue

Aortic and pulmonary valves should be sized at the annulus and the internal diameter recorded in millimetres. The sizing should be performed after the antibiotic decontamination.

The length of the aortic conduit, main pulmonary artery and right and left pulmonary artery remnants should be recorded.

Detailed description of the condition of the valve must be recorded in the donor processing records, which should include a grading system or schematic representation. Under no circumstances should a valve conduit be turned inside out for inspection purposes.

Valve descriptions and evaluation must accompany the allograft distribution and be made available to the surgeon on request.

Heart valves and vessels should be processed using a disinfection process which has been shown to produce decontaminated tissues.

Disinfection time must not exceed that specified in a validated disinfection regime.

Bacteriological testing of tissue

Where tissues are exposed to a decontamination step an assessment of the bacteriological status prior to decontamination must be performed.

Processed tissue must be subjected to bacterial (including *Mycobacterium tuberculosis*) and fungal testing using validated techniques. Each bank should develop a list of exclusion criteria based on type and number of contaminating organisms prior to and following decontamination.

Cryopreservation

Currently accepted optimal procedures involve controlled rate cooling of cardiovascular tissues in the presence of cryoprotectant.

Currently no recommendations can be made for non-cryopreserved valves or other cardiovascular tissues.

Storage and thawing of cardiovascular tissues

For material stored at -135°C or below, if during thawing the tissue is warmed too rapidly between the storage temperature and -100°C , fractures can occur. A validated method of thawing (e.g. on dry ice) must be used to minimize the risk. This must ensure that the valve has reached a temperature above -100°C before thawing in a 37°C water bath.

Material stored at -135°C , which is subsequently transported with solid carbon dioxide (-79°C), should be maintained in a mechanical freezer (at -80°C) if not used immediately. Thereafter, a maximum storage time of six months will pertain.

Distribution

Cryopreserved valves and vessels must be transported either in solid carbon dioxide at -79°C or in a container maintaining a temperature of -135°C or lower. Cardiovascular tissue must not be submerged in liquid nitrogen during transport.

23.11 Skin retrieval and processing

Skin retrieval

Skin sites should be shaved if necessary and treated with an anti-microbial agent such as chlorohexidine.

Samples of skin must be cultured for aerobic and anaerobic bacteria and fungi prior to and following decontamination.

Skin processing

Skin can be processed to provide an acceptable graft in a number of ways. These include cryopreservation, high concentration glycerolization and other methods. The specification for any skin product should clarify the required properties.

References

1. *Health Technical Memorandum (HTM) 2010 Sterilization* www.nhsestates.gov.uk.
2. *Health Technical Memorandum (HTM) 2030 Washer-Disinfectors* www.nhsestates.gov.uk.
3. *Health Technical Memorandum (HTM) 2031 Clean Steam for Sterilization* www.nhsestates.gov.uk.
4. Medicines and Healthcare products Regulatory Agency (2007) *Rules and Guidance for Pharmaceutical Manufacturers and Distributors*, Pharmaceutical Press, ISBN 978-0-85369-719-0.
5. EC Guide to Good Manufacturing Practice Revision to Annex 1 (2003) Ad Hoc GMP Inspections Services Group http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/vol-4/pdfs-en/revan1vol4_3.pdf



Chapter 24

Haemopoietic progenitor cells

The cellular therapy products described in these guidelines are referred to as haemopoietic progenitor cells HPC-A, HPC-M and HPC-C to denote their collection by apheresis or from marrow and cord blood respectively or as therapeutic cells (TC), the most commonly used of which is TC-T cells (T) often referred to as donor lymphocyte infusions (DLI).

Introduction

A number of important documents have become available since the last publication of this chapter. These include the European Union Directive on Tissues and Cells (2004/23/EC), its associated Commission Directives (2006/17/EC; 2006/86/EC) and the Third Editions of the FACT-JACIE and NETCORD-FACT Standards. Accordingly these guidelines have been updated. They have also been abbreviated with appropriate cross-reference to the new Directives and Standards. Some sections which contain important practical information, not readily available elsewhere, are unabridged. The Human Tissue Act and Codes of Practice issued by the Human Tissue Authority are referred to where appropriate. The bibliography has been grouped according to its origin.

The guidelines in this chapter apply to the donation, collection, testing, processing, cryopreservation, storage and distribution of haemopoietic progenitor cells (HPC) and therapeutic cells (TC) within the UK Blood Transfusion Services (UKBTS). HPCs include bone marrow, peripheral blood and cord blood progenitor cells. The guidelines must be read in conjunction with the other sections of the book including those that apply to quality systems, quality assurance and to testing of donors. These guidelines are applicable to stem cell donor registries and to bone marrow, peripheral blood and cord blood collection and processing facilities.

European Union Directives

1. Directive 2004/23/EC of the European Parliament and Council on setting standards of quality and safety for the donation, procurement, testing, processing, preservation, storage and distribution of human tissues and cells.

www.transfusionguidelines.org.uk

2. Commission Directive 2006/17/EC implementing Directive 2004/23/EC of the European Parliament and Council as regards certain technical requirements for the donation, procurement and testing of human tissues and cells

www.transfusionguidelines.org.uk

3. Commission Directive 2006/86/EC implementing Directive 2004/23/EC of the European Parliament and Council as regards traceability requirements, notification of severe adverse reactions and events and certain technical requirements for the coding, processing, preservation, storage and distribution of human tissues and cells.

www.transfusionguidelines.org.uk

4. Department of Health Statutory Instrument No. 1523. Human tissue (quality and safety for human application) regulations 2007.

(The EU Directive on Tissues and Cells and its associated Commission directives are referred to collectively as the EU Directive on Tissues and Cells in this chapter.)

5. Directive 2001/83/EC of the European Parliament and Council on the Conduct of Clinical Trials

<http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/homev1.htm>

International Standards

6. *Standards for Haematopoietic Progenitor Cell Collection, Processing and Transplantation*. Third Edition (2007) from the Foundation for the Accreditation of Cell Therapy (FACT) and the Joint Accreditation Committee of ISCT-Europe and EBMT (JACIE). www.jacie.org
7. *JACIE Accreditation Manual*. Second Edition 2003 (adapted 2005) available at www.jacie.org.
8. NETCORD-FACT *International Standards for Cord Blood Collection, Processing, Testing, Banking, Selection and Release* 3rd Edition 2007, available from www.factwebsite.org.
9. World Marrow Donor Association (WMDA) *Standards*, March 2005, available at www.worldmarrow.org

Human Tissue Authority

10. The Human Tissue Act 2004 (except Scotland), ISBN 0 10 543004 8 www.hta.gov.uk
The Human Tissue Act 2006 (Scotland), ISBN 0-10-590094-X available at www.show.scot.nhs.uk
11. Human Tissue Authority. Directions given under the Human Tissue Act 2004: 001/2006 www.hta.gov.uk
12. Human Tissue Authority (HTA): Codes of Practice for Consent (Code 1), for Donation of Organs, Tissues and Cells (Code 2), for Removal, Storage and Disposal of Human Organs and Tissues (Code 5), for Donation of Allogeneic Bone Marrow and Peripheral Blood Stem Cells for Transplantation (Code 6) and for Import and Export of Human Bodies, Body Parts and Tissue (Code 8) available at <http://www.hta.gov.uk>

Histocompatibility and Donor Selection Documents

13. Hurley, C. K. (1999) 'Histocompatibility testing guidelines for haematopoietic stem cell transplantation using volunteer donors: report from the World Marrow Donor Association. Quality Assurance and Donor Registries Working Groups of the World Marrow Donor Association'. *Bone Marrow Transplant*. **24**(2), pp119–21.
14. 'Standards for histocompatibility testing' (2005) available at the European Federation for Immunogenetics (EFI) standards available at www.efiweb.org.
15. National Marrow Donor Program (USA) *Standards*, 19th Edition, available at www.marrow.org
16. Joint UKBTS/NIBSC Professional Advisory Committee's (JPAC) *Donor Selection Guidelines* available at www.transfusionguidelines.org.uk

24.1 Terminology

For the purposes of these guidelines, the terms shall, will, or must mean that the guideline is to be complied with at all times. The terms may and should indicate an activity that is recommended or advised, but for which there may be effective alternatives.

The principles of quality assurance as outlined in Chapter 2 apply. The cellular therapy products described in these guidelines are referred to as haemopoietic progenitor cells HPC-A, HPC-M and HPC-C to denote their collection by apheresis or from marrow and cord blood respectively or as therapeutic cells (TC), the most commonly used of which is TC-T cells (T) often referred to as donor lymphocyte infusions (DLI).

24.2 Policy and procedure requirements

- 24.2.1 Policies and procedures must include all aspects of the operation including donor selection, assessment, consent, microbiological testing, collection, labelling, system of numbering, processing, quality management and improvement, proficiency testing, storage, including alternative storage strategies if the primary storage device fails, transportation, outcome analysis, audits, expiry dates, emergency and safety procedures, equipment and supplies, maintenance and monitoring, cleaning procedures, personnel training, disposal of medical and biohazard waste, release procedures, including criteria for exceptional release, references, tolerance limits, corrective actions, recall, returns and discard policy.
- 24.2.2 The medical director/advisor and laboratory director/manager must review and approve all policies, procedures and research protocols annually to determine that they are clinically appropriate and consistent with the requirements of users of the service. They should seek to maximize safety for both donors and recipients.
- 24.2.3 Procedures carried out by third parties, e.g. donor assessment and harvesting centres, clinical transplant units, and testing laboratories must be described by written agreements. These must define and document relationships between the facility and the third party. The details of the agreement including responsibilities must be clearly specified, documented and agreed between parties. The agreement must include an option for audit of procedures carried out by the third party. Documented procedures to review these agreements should be in place.
- 24.2.4 All clinical and laboratory facilities should conform to the relevant EU Directives and both FACT-JACIE and NETCORD-FACT Standards as appropriate. Laboratories must participate in appropriate recognized external quality assurance schemes. All clinical and laboratory facilities must be compliant with the requirements of the EU Clinical Trials Directive. Documentation of all research protocols performed by the facility must be maintained. This must include copies of research and ethics committee approvals for all relevant procedures.

24.3 Safety requirements

- 24.3.1 Each HPC processing facility must be operated in a manner to minimize risks to the health and safety of employees, donors and recipients. Suitable facilities and equipment must be available to maintain safe operations.
- 24.3.2 There must be procedures for microbiological, chemical and radiation safety, as appropriate, and a system for monitoring training and compliance.
- 24.3.3 HPC and TC collections must be handled and discarded with precautions that recognize the potential for exposure to infectious agents.

24.4 Adverse events and reactions

- 24.4.1 Facilities must ensure that there is a system in place to detect, report, investigate, document and follow up all errors, adverse events and reactions affecting donors and those which could affect the quality of HPC components and which may be attributable to their collection and processing.

- 24.4.2 These systems must also apply to any serious adverse events and reactions observed after administration of HPC components.
- 24.4.3 Documentation of these events shall be reviewed by the facilities' Directors as appropriate.
- 24.4.4 The responsible person/designated individual must ensure that these events are notified to the HTA.
- 24.4.5 Facilities must ensure that appropriate corrective actions are taken and that recall procedures are in place to enable it to recall any component(s) related to serious adverse events and reactions.

24.5 Donor selection, consent and testing

24.5.1 Allogeneic HPC-M donors

General principles

- Registries must have detailed policies and procedures for the testing and assessment of donors of HPC and TC. These must be in accordance with the requirements of the EU Directive on Tissues and Cells, FACT-JACIE Standards and WMDA Guidelines.
- Counselling – relevant information must be given to potential donors at appropriate times. This shall include an explanation of the risks of the procedure, benefits for the intended recipient tests to be performed to protect the health of the donor and recipient; the policy of informing donors of significant abnormal results; the right to withdraw from the donation; the risk of death for the recipient if the donor withdraws after the recipient's conditioning therapy has started; anonymity policy; insurance arrangements; reimbursement of expenses.
- Consent – the donor must be competent to give and have given valid consent before conditioning therapy is initiated in the recipient. Consent must be obtained in accordance with the requirements of the Human Tissue Act and the HTA's Codes of Practice on consent and donation of allogeneic bone marrow and peripheral blood stem cells for transplantation.

Medical history, physical examination and testing

- The donor medical assessment must be performed according to the requirements of the EU Directive on Tissues and Cells, FACT-JACIE Guidelines and WMDA Guidelines.
- Anonymity must be maintained between BBMR/WBMDR donors and recipients for life in accordance with the requirements of EU Directive 2004/23/EC. The BBMR and WBMDR must have robust policies for donor follow-up in accordance with the requirements of the WMDA, FACT-JACIE and NETCORD Standards and the relevant EU Directives.

24.5.2 Allogeneic HPC-A donors

HPC-A may be collected after mobilization with a licensed G-CSF preparation.

The requirements of Section 24.5.1 also apply. A donor of HPC-A must be found fit for both apheresis and G-CSF administration and may also be assessed for fitness to undergo bone marrow harvest in the event of failure to mobilize stem cells.

24.5.3 Autologous HPC-M and HPC-A donors

The assessment and counselling of patients is not within the scope of these guidelines. However, consent must be obtained in accordance with the requirements of the HTA. The requirements for processing, preservation, storage and testing of autologous donations are described in Sections 24.8, 24.9 and 24.10.

24.5.4 Repeat donations of allogeneic HPC-A, HPC-M or first or repeat donations of TC

These are requests either for further donations of HPC, for the same or different patient, from donors who have in the past given an HPC donation or for a TC donation for the same patient where an HPC donation has already been given. Individual assessment of each request is required. This must include further medical assessment with appropriate testing, counselling and consent.

24.5.5 Allogeneic HPC-C donors

- HPC Facilities/Cord Blood Banks must have detailed policies and procedures for the assessment and testing of donor mothers and infant donors of HPC-C. These must be in accordance with the requirements of the EU Directive on Tissues and Cells, NETCORD-FACT Standards and WMDA Guidelines.
- Maternal assessment must be performed by appropriately trained staff, according to the requirements of the EU Directive on Tissues and Cells, NETCORD-FACT Standards and WMDA Guidelines.
- Infant assessment must be performed by appropriately trained staff, according to the requirements of the EU Directive on Tissues and Cells, NETCORD-FACT Standards and WMDA Guidelines.
- Testing requirements, see section 24.10. Maternal samples taken at time of collection of the HPC-C (day 0 to +7) shall be tested in accordance with the requirements of the EU Directive on Tissues and Cells, NETCORD-FACT Standards and WMDA Guidelines.
- Consent. Detailed information must be provided to potential donor mothers prior to requesting consent, in terms and translations relevant to the mother. Consent for collection must be obtained prior to harvest of the cord blood. Consent must be obtained in accordance with the requirements of the Human Tissue Act, the HTA's Codes of Practice for consent and donation of organs, tissue and cells for transplantation, EU Directive on Tissues and Cells and NETCORD-FACT Standards.

24.6 Collection facilities for HPC-A, HPC-M, HPC-C and TC

24.6.1 General

HPC-A, HPC-M, HPC-C and TC should only be collected in a hospital facility or blood service apheresis unit with appropriate experience (see Chapter 6, Component donation: apheresis) and which meets the standards required by the EU Directive on Tissues and Cells, FACT-JACIE Standards and NETCORD-FACT Standards as appropriate. The facility will be headed by a medical director/advisor and a collection facility director with appropriate experience as described in the above standards. The collection facility shall have an organisational structure and operational procedures appropriate for the activities carried out. There must be an organisational chart which clearly defines accountability and reporting relationships. The medical director/advisor shall have responsibility and authority for all clinical aspects of the programme including compliance with national and local guidelines as well as ensuring compliance with regulatory requirements.

The collection facility director is responsible for the operational management and technical aspects of the service. The medical director/advisor may also act as the collection facility director. There shall be adequate numbers of staff whose training and competency to perform the assigned procedures must comply with the requirements of the EU Directive on Tissues and Cells, FACT-JACIE Standards and NETCORD-FACT Standards.

There must be a documented quality management system applied to all activities and a designated quality manager.

There must be a responsible person/designated individual as defined by the EU Directive on Tissues and Cells/Human Tissue Act.

24.6.2 HPC-M donors should be assessed and managed in accordance with the aforementioned guidance. Specific points of importance are:

- A consultant anaesthetist should take responsibility for the care of the donor during the harvest procedure
- There should be intensive care (or equivalent) and resuscitation facilities on-site

24.6.3 HPC-A donors should be assessed and managed in accordance with the aforementioned guidance. Specific points of importance are:

- Physicians prescribing human growth factors must be experienced in their use.
- Donors and recipients undergoing progenitor cell mobilization must have access to advice and medical supervision 24 hours a day.

Venous access

- Peripheral veins should ordinarily be used for venous access for donors.
- Where access via peripheral veins is not feasible and appropriate consent is obtained, central venous catheterization (e.g. via the femoral or other route) may be considered.
- The placing of central catheters should only be undertaken in hospital facilities with access to intensive care and radiology facilities by highly trained staff who regularly perform this procedure.
- Collection centres must ensure that the adequacy of central venous catheterization has been confirmed.

24.6.4 HPC-C collections should be managed in accordance with the aforementioned guidance. Specific points of importance are:

- For unrelated collections there must be a written agreement defining the responsibilities and expectations between the Cord Blood Bank and the Obstetric Department of the collection hospital.
- For directed allogeneic or autologous collections, harvested in a non-fixed collection facility, there must be a written agreement related to HPC-C collection, transport, processing, testing, storage and release, between the referring consultant and the HPC facility.
- Delivery practices must not be modified in an attempt to facilitate HPC-C collections.
- There must exist a documented system for identification of the HPC-C product and for confirming the link with the mother.

24.7 Component definitions

DEFINITIONS

Unmanipulated	HPC as obtained at collection and not subject to any manipulation.
Manipulated	Subjected to an ex vivo process that selectively removes/enriches, expands or functionally alters HPCs.
● Minimally Manipulated	Processing that does not alter the relevant biological characteristics of cells or tissues.
● More than Minimally Manipulated	Processing that does alter the relevant biological characteristics of cells or tissues.

PRODUCTS

HPC, Apheresis (HPC-A)	HPC collected from the peripheral blood using an apheresis technique usually after receiving a haemopoietic growth factor.
HPC Marrow (HPC-M)	HPC aspirated from the iliac crests, sternum or other bones.
HPC Cord Blood (HPC-C)	HPC-C from umbilical cord +/- placenta at time of delivery.
Therapeutic Cells (TC)	Cell products harvested or manufactured for the purpose of providing therapeutic benefit. TC, T Cells (TC) TC, Dendritic Cells (DC) TC, Marrow TC, Whole Blood TC, Apheresis TC, T Regulatory Cells (T-Reg) TC, Tumour-derived TC, Mesenchymal Stem Cell (MSC) TC, Natural Killer (NK) TC, Cytotoxic Lymphocytes (CTL) Other Therapeutic Cells

PRODUCT MODIFICATIONS

Plasma Reduced	Cells remaining after a portion of plasma has been depleted by sedimentation or centrifugation using devices, supplies and techniques validated for this purpose.
Plasma & RBC reduced	Cells remaining after depletion of mature erythrocytes and a portion of plasma by sedimentation and/or centrifugation using devices supplies and techniques validated for this purpose
RBC Reduced	Cells remaining after depletion of mature erythrocytes by sedimentation and/or centrifugation using devices, supplies and techniques validated for this purpose.
B Cell Depletion	Cells processed by negative selection for B Lymphocytes.
T Cell Depletion	Cells processed by negative selection for T Lymphocytes.
Buffy Coat enriched	Cells remaining after depletion of mature erythrocytes and plasma by sedimentation or centrifugation using devices, supplies and techniques validated for this purpose.
Density enriched	Primarily mononuclear cells remaining after depletion of mature erythrocytes, polymorphonuclear cells and plasma by separation of the cell on the basis of density. This is achieved using devices or reagents validated for the separation of cells based on density.
Cryopreserved	Cells frozen using devices, supplies and techniques validated to maintain viability.

CD34 selected	Enriched cells processed by positive selection for CD34 antigen bearing cells.
Ex vivo expanded	Cells that have been cultured in vitro for the purpose of producing and/or enriching for a specific functional subset.
Tumour Cell Depletion	Cells processed by negative selection for Tumour Cells.
Gene manipulated	Cells that have been processed to alter their own genes or introduce new genetic material.

24.8 Haemopoietic progenitor cell processing standards

24.8.1 Personnel and facilities

Processing facilities must comply with the requirements of the EU Directive on Tissues and Cells, FACT-JACIE Standards and NETCORD-FACT Standards. There shall be a medical director/advisor who will have responsibility and authority for all clinical aspects of the programme including compliance with national and local guidelines as well as ensuring compliance with regulatory requirements.

There will be a laboratory director/manager who is responsible for the operational management and technical aspects of the service. There should be adequate numbers of staff whose training and competency to perform the assigned procedures must comply with the requirements of appropriate regulations and standards.

There must be a responsible person/designated individual as defined by the EU Directive on Tissues and Cells/Human Tissue Act.

The HPC processing facility shall have an organisational structure and operational procedures appropriate for the activities carried out. There must be an organisational chart which clearly defines accountability and reporting relationships. There must be a documented quality management system applied to all activities and a designated quality manager.

24.8.2 Procedures

- Before processing there should be a written request from the transplant physician. This is not required for unrelated CB collections.
- Processing should be performed according to written procedures and policies. All procedures must be validated prior to implementation. Aseptic technique must be employed. Any deviation from such written procedures shall be documented and reviewed.
- Before material is accepted from a third party including receipt from abroad the laboratory accepting the donation should, wherever possible, ensure that standards equivalent to those in UK guidelines, have been met. Material should be inspected upon receipt and the condition of the product recorded.
- Where appropriate the HPC donation should be passed through a sterile non-reactive aggregate filter to remove fat, clots or bone spicules that may be present. A closed system must be used wherever practical.
- Processing and transplant facilities must agree and validate the adequacy of dose (total nucleated cells, mononuclear cells, CD34 positive cells and/or CFU-GM as appropriate for each source of HPC) required to achieve reliable and sustainable engraftment.

Tests for cell dose and viability should be performed as in Section 24.11.

24.9 Storage of cellular therapy products

24.9.1 Policies **must** be in place for the storage of all material whether or not destined for cryopreservation, e.g. HPC-M undergoing red cell depletion and for other HPCs prior to cryopreservation. Details should be specified for all types of storage conditions. These should cover:

- labelling
- primary and secondary containers
- storage temperature and duration
- cell concentration

Briefly, donations with a cell concentration above $200 \times 10^9/L$ must be diluted to less than $200 \times 10^9/L$, preferably with autologous plasma, and placed at $4^\circ C \pm 2^\circ C$ if they are for liquid storage and/or are not being processed immediately. The final concentration after addition of the cryoprotectant must be less than $100 \times 10^9/L$.

- transport if appropriate

24.9.2 Duration

Facilities storing HPC components shall establish policies for the duration and conditions of storage and indications for discard. Patients, donors and associated transplant centres should be informed about these policies and consent obtained where appropriate.

24.9.3 Alarm systems

- Storage devices shall have alarm systems that are continuously active.
- Alarm systems shall have audible signals.
- If laboratory personnel are not always present in the immediate area of the storage device, a remote alarm device shall be required at a location staffed 24 hours a day. Alternatively an auto-dial facility connecting to an on-call member of staff may be satisfactory.
- Alarms shall be set to activate at temperatures or an unsafe level of liquid nitrogen to allow time to salvage components.
- There shall be a written procedure to be followed if the storage device fails.
- A procedure for notifying laboratory personnel should be in place.
- Alarm systems shall be checked periodically for function.
- Additional storage devices of appropriate temperature shall be available for component storage if the primary storage device fails.

24.9.4 Inventory control

There shall be an inventory control system to enable component and quality control vials to be located. It should include the donor name or unique identifier, date of collection, type of storage device and location within it, stating number of containers and vials and number issued, dates of issue and numbers of containers and vials remaining.

24.9.5 Cryopreservation

Archive samples. Aliquots of the HPC component, processed and stored under the same conditions as the HPC component, must be available for additional testing as necessary.

- Methods should be validated, taking into account critical pre-freeze variables such as temperature, duration of storage, cell density and type of cryoprotectant.

- A secondary container, 'double bagging', must always be used to prevent cross-contamination between donations and to effectively quarantine the unit.
- The containers must be clearly and unambiguously labelled using labels that have been validated for use under the required storage conditions. The data on the labels must be in accordance with FACT-JACIE and NETCORD-FACT requirements.
- Cryopreservation of the HPC product must be with an established cryoprotectant, e.g. 10% DMSO, used in a validated procedure with defined times and temperatures of exposure to specified concentrations.
- Established conditions of time and temperature of exposure of the HPC component to the cryoprotectant must be observed. These must be specific to the cryoprotectant system used. Validated storage conditions for the cryoprotectant must be observed.

Frozen HPCs should be stored at a sufficiently low temperature to ensure recovery of living cells after the intended preservation period. If indefinite storage is required a temperature below -150°C should be used.

It is recommended that the vapour phase of liquid nitrogen is used to reduce the risk of cross-contamination. It is recognized, however, that this is associated with a greater temperature fluctuation and measures should be taken to ensure that the paragraph above applies. Some facilities may employ total or partial immersion in liquid phase to store HPC donations. Whatever method of storage is used it must always be assumed that liquid nitrogen is microbially contaminated and secondary enclosure must be employed.

For vapour phase the storage vessels should be fitted with a minimum of two temperature probes that are linked to a remote central monitoring system manned continuously. For liquid phase storage the vessel should be fitted with a minimum of a single probe. Records must be kept of these temperatures.

If liquid nitrogen refrigeration is used an automatic filling mechanism or a standardized manual procedure must be provided to ensure and document that adequate levels of liquid nitrogen are maintained.

24.10 Testing of haemopoietic progenitor cell donors and components including therapeutic cells

24.10.1 Infectious disease marker testing

This must be done in accordance with the requirements of the EU Directive on Tissues and Cells, FACT-JACIE and NETCORD-FACT.

The current requirements include testing for HIV1/2 antibodies, HTLV I/II antibodies (high risk individuals only), HBsAg, HBc antibodies, HCV antibodies and a test for syphilis. Additional testing may be required in some cases e.g. for malaria and toxoplasmosis.

Table 24.1 Requirements for the timing of testing

Test	ALLO HPC-A/HPC-M/TC	AUTO HPC-A/HPC-M	HPC-C DONOR MOTHER	HPC-C
ABO + RhD	Test at each donation	Test at first donation		d0 to d+7
Anti- HIV 1/2 antibody	d-30 to d0	d-30 to d0	d-7 to d+7	prior to release
Anti- HCV antibody	d-30 to d0	d-30 to d0	d-7 to d+7	prior to release
Anti- HTLV I/III(pooled) antibody	d-30 to d0	d-30 to d0	d-7 to d+7	prior to release
HCV RNA (pooled)	d-30 to d0	d-30 to d0	d-7 to d+7	prior to release
HBs Ag	d-30 to d0	d-30 to d0	d-7 to d+7	prior to release
Anti-HBc antibody	d-30 to d0	d-30 to d0	d-7 to d+7	prior to release
CMV	d-30 to d0	d-30 to d0	d-7 to d+7	prior to release
Pregnancy Test	-7d preconditioning			
Malaria	Where clinical indication	Where clinical indication	Where clinical indication All mothers where there is risk.	
Haemoglobinopathy ie Sickle Cell	Where clinical indication	Where clinical indication		Prior to release
Syphilis screen*	d-30 to d0	d-30 to d0	d-7 to d+7	
Bacteriology Testing	If manipulation	If manipulation		On final product
FBC	Before each apheresis procedure	Before each apheresis procedure		Pre & post process

* Confirmatory tests should be performed if screen positive

Additional tests must be undertaken for quarantined HPC-C products where a d180 repeat test has not been done. The following tests should be performed to permit release:

HIV PCR pooled/single

HCV PCR pooled/single

HBV PCR single

Mechanisms should be in place to ensure that archived material /samples can be retested at the time of issue of donation for all current markers of infection including the latest generation of assays.

24.10.2 HLA typing

- At initial registration: HLA-A, -B, -DR type by a CPA and European Federation for Immunogenetics (EFI) accredited laboratory. As a minimum these antigens should be defined at low/medium resolution level using DNA techniques.
- Confirmatory typing: Must be performed on a sample drawn independently of that used for initial registration. HLA-A, -B, -C, -DRB3, -DRB4, -DRB5 and -DQB1 types should be defined, at a minimum, to medium resolution using DNA techniques. HLA-

DRB1 should be defined to the allele level by DNA techniques. High/allele resolution typing for HLA-A, -B, -C, -DRB3, -DRB4, -DRB5, -DQB1 and -DPB1 can also be performed as required by the transplant protocol.

For cord blood donations it is recommended that a maternal sample is HLA typed to confirm identity. High resolution typing of cord blood units shall take place when requested by a transplant centre. In cord blood banking, prior to the release of a CB unit for transplantation a sample obtained from a contiguous segment of the cryopreserved CB unit must be tested to verify HLA type and STR (short tandem repeat) is also performed according to NETCORD standards.

24.10.3 ABO and Rh D typing

For allogeneic donors of HPC-A and HPC-M ABO and RhD typing must be performed on samples taken from the donor or cell therapy component at the time of each collection. For autologous donors of HPC-A and HPC-M, ABO and RhD typing must be performed on samples taken from the donor or cell therapy component at the time of first collection. For HPC-C the ABO and RhD type of each donation shall be determined.

24.10.4 Clonogenic assays

Clonogenic assays, e.g. CFU-GM may be undertaken as part of a quality programme or when specifically indicated or requested by the transplant physician. Consideration should be given to performing surrogate tests for viability prior to conditioning on a representative archive sample of any cryopreserved HPC components. For cord blood units CD34+ cells should be enumerated according to NETCORD standards and progenitor cell assays should be assessed on a thawed sample before release of the unit for transplant.

24.10.5 Sterility

Bacteriological and fungal screening employing aerobic and anaerobic conditions must be performed on the final HPC component after processing and before cryopreservation, unless validation studies demonstrate that bacteriological screening of waste processing material, such as plasma or erythrocytes, are equivalent to screening of the final product. All positive cultures should be subsequently identified and antibiotic sensitivities performed if the material is to be put to clinical use.

24.10.6 Test samples

Archival samples must be stored for reference and any future testing that may be required as described in the EU Directive on Tissues and Cells, FACT-JACIE Standards and NETCORD-FACT Standards. Documentation must be kept to ensure security and accurate retrieval of the stored samples when required.

- to maintain viability (below – 150°C)
- to obtain suitable material for the preparation of 50 ug DNA

24.11 Labelling, packaging, transportation and temperature controls

The requirements for these are described in the EU Directive on Tissues and Cells, FACT-JACIE Standards and NETCORD-FACT Standards and the requirements for labelling are summarised in the tables below.

Table 24.2 Label content adapted from FACT-JACIE

Element	Partial label	Label at completion of collection	Label during processing	Label at completion of processing	Label at distribution	Inner and outer shipping container
Unique identifier of product	AF	AF	AF	AF	AF	
Proper name of product	AF	AF	AF	AF	AF	
Recipient name and identifier	AF (if applicable)	AF (if applicable)	AF (if applicable)	AF (if applicable)	AF (if applicable)	
Date, time collection ends and (if applicable) time zone		AF		AC	AC	
Approximate volume		AF		AC	AC	
Name and volume or conc. of anticoagulant and other additives		AC		AC	AC	
Donor identifier and (if applicable) name		AF		AT	AT	
Identity and address of collection facility or donor registry		AC		AC	AC	
Recommended storage temperature		AT		AT	AT	
Biohazard label		AC (if applicable)		AC (if applicable)	AC (if applicable)	AC (if applicable)
Identity and address of processing facility				AF	AF	
ABO and Rh of donor				AC	AC	
RBC compatibility testing results				AC	AC (if applicable)	
Statement "Properly identify intended recipient and product"				AC	AC	
Statement "Warning; this product may transmit infectious agents"				AF	AF	
Expiration date				AF (if applicable)	AF (if applicable)	
Expiration time				AF (if applicable)	AF (if applicable)	
Statement "For autologous use only" or Statement "For use by intended recipient only"				AF (if applicable) AF (if for allogeneic recipient)	AF (if applicable) AF (if for allogeneic recipient)	

Table 24.2 Label content adapted from FACT-JACIE – *continued*

Element	Partial label	Label at completion of collection	Label during processing	Label at completion of processing	Label at distribution	Inner and outer shipping container
Statement “Do not irradiate”				AT	AT	
Statement “Not for infusion” including reason				AT (if applicable)	AT (if applicable)	
Name and address of receiving institution						AF
Name and phone number of contact person at receiving institution						AF
Statement “Medical Specimen”						AF
Statement “Do not X-Ray”						AF
Name, address and phone number of shipping facility						AF

AF = affixed, AT = attached or affixed, AC = accompanying or attached or affixed

Table 24.3 Label content for HPC-C adapted from NETCORD-FACT

Label Element	Partial Label	Label at completion of collection	Shipping container labelling for transport from collection	Label at completion of processing	Label at CB unit release	Dry Shipper Labelling at issue
Unique numeric or alphanumeric identifier	AF	AF		AF	AF	
Proper name HPC, Cord Blood	AF	AF	AF	AF	AF	
Product modifiers				AC	AC	
Statement "Directed Donor" (directed allogeneic & autologous HPC-C units)	AF	AF		AF	AF	
Statement "Autologous Use Only." (autologous HPC-C units)	AF	AF		AF	AF	
Collection centre identifier		AF	AT			
Date of collection		AF		AC	AC	
Time of collection		AC				
Name & volume or concentration of anticoagulant & other additives.		AF		AC	AC	
Recommended storage temperature		AT		AF	AF	
Donor name (directed allogeneic & Autologous HPC-C units)		AF		AF	AF	
Recipient's name, unique identifier or family (directed allogeneic & autologous HPC-C units) – if applicable		AF			AF	
Volume or weight of the HPC-C unit at the end of collection.				AC	AC	
Volume or weight of the HPC-C unit at end of processing				AC	AC	
Date of cryopreservation				AC	AC	
ABO group & Rh type				AC	AC	
HLA phenotype				AC	AC	

Table 24.3 Label content for HPC-C adapted from NETCORD-FACT – *continued*

Label Element	Partial Label	Label at completion of collection	Shipping container labelling for transport from collection	Label at completion of processing	Label at CB unit release	Dry Shipper Labelling at issue
Number of nucleated cells post processing.				AC	AC	
Gender of HPC-C infant donor				AC	AC	
Identity of the CBB				AF	AF	
Statement “Properly Identify Intended Recipient & Product”					AT	
Statement “For Use By Intended Recipient Only” (allogeneic HPC-C units)					AT	
A statement indicating that leukoreduction filters should not be used					AT	
Statement “Do Not Irradiate”					AT	
Statement “For Nonclinical Use Only” (if applicable)					AT	
Biohazard labels -if applicable		AF	AF	AT	AT	
Date of distribution					AC	AF
Shipping facility name, address, phone number			AF			AF
Receiving facility contact details			AF			AF
Identity of person or position responsible for receipt of shipment			AF			AF
Statement “Do Not X-Ray”						AF
Statement “Medical Specimen”, “Handle With Care”						AF
Statement indicating HPC-C for transplantation						AF
Shipper handling instructions						AF

AF = affixed, AT = attached or affixed, AC=accompanying or attached or affixed

24.12 Release

Prior to HPCs being cleared for issue, all relevant records, including donor records, processing and storage records, and post-processing quality control tests must have been reviewed, approved and documented as acceptable by the individual(s) responsible according to the relevant local SOPs. Responsibility for setting policies for exceptional release and for issuing products on concession resides with the medical director/advisor.

For cord blood donations release occurs at two stages:

- (i) Following completion of testing and donor selection when donations are formally banked and made available for search
- (ii) At issue for transplantation

24.13 Transportation

The methods used to transport frozen components to the hospital must have been shown to maintain integrity of the component and to provide the temperature specified for storage. Liquid nitrogen dry shippers are suitable. Only components that were stored either partially or completely submerged in liquid nitrogen may be submerged in liquid nitrogen for transport.

24.14 Thawing and infusion

- The units should be thawed in a manner that has been established as appropriate for the overall preservation technique.
- Infusion documentation shall facilitate tracking of the product from the donor to recipient. Records must demonstrate that before cells are released the product specification is met and verified according to a written procedure by a person authorised by the Responsible Person/Designated Individual. For clinical use of a product that has not met its specification, exceptional release specific authorisation must be given by the facility Medical Director or designee.
- A component infusion form shall be issued with the product and completed for each component infused. A copy should be returned to the processing laboratory.
- There must be an effective recall procedure in place defining responsibilities and actions to be taken including notification to the competent authority (HTA). Procedures must be in place for the documentation of returned products, defining acceptance criteria into the inventory.

24.15 Disposal of haemopoietic progenitor cells

- Prior to collection there shall be a written agreement between the processing facility and the donor defining the length of storage and circumstances for disposal or transfer of cellular therapy products to an alternative facility.
- There must be written documentation of the recipient's death or no further need for any component before it is discarded. Written instructions from the transplant physician should be obtained. Appropriate prospective consent for discard should have been obtained.
- The records for discarded components must indicate the component discarded, date of discard and method of disposal.
- The medical director/advisor of the processing facility, in consultation with the patient's transplant physician, must approve of component discard and method of disposal. If the patient is still alive their consent for disposal of the components must have been obtained.
- The method of disposal and decontamination must meet the UK laws, current codes, rules and regulations for disposal of biohazardous materials.

24.16 Records

24.16.1 General requirements

- All patient records and results should be maintained to the requirements of the Caldicott report (1997) and the Data Protection Act (1998).
- Records must be made concurrently with each step of the harvesting, processing, testing, cryopreservation, storage, issue and transplant or disposal of each component in such a way that all the steps may be accurately traced from donor to recipient.
- All records and communications between the collection, processing and transplant centres must be regarded as privileged and confidential. Safeguards to assure this confidentiality must be established and followed.
- Records pertaining to cellular therapy products shall be accurate, legible, indelible and maintained for a minimum of 10 years.

24.16.2 Records to be maintained

The requirements for these are described in the EU Directive on Tissues and Cells, FACT-JACIE Standards and NETCORD-FACT Standards. Records of the following must be kept:

- Donor and patient details
- Collection and processing
- Storage, issue and administration
- Compatibility testing
- Quality control
- Personnel, training, continued education, competency testing
- Incidents, errors and corrective action taken

24.16.3 Records in cases of divided responsibility

If 2 or more facilities participate in the collection, processing or distribution of the product, the records of the processing facility shall show clearly the extent of its responsibility.

Index

- ABO typing 37, 38
- adverse events and reactions 22, 29–30
- air quality 17, 19
- alarm systems 20, 35
- amnion donation 8, 9
- antibiotic disinfection 15
- antibody testing 8, 36, 37
 - cadaver donors 8, 10
- apheresis *see* haemopoietic progenitor cells, apheresis (HPC-A)
- aseptic processing facilities, requirements 15–17
- audit trail 5
- autologous donations 10–11, 30–31

- B cell depletion, definition 33
- Bacillus niger* var. *subtilis* 18
- bacterial and fungal contamination
 - policies 15
 - screening of HPC components 37, 38
 - testing of tissue 18, 24
- bacteriostasis and disinfection 15
- blood samples, from cadaver donors 9–10
- bone *see* skeletal tissue
- bone marrow *see* haemopoietic progenitor cells, marrow (HPC-M)
- buffy coat enriched, definition 33

- cadaver donors
 - follow up of contacts 10
 - infants 10, 11
 - information for next of kin 6
 - medical history 6, 7
 - reconstruction 14
 - skeletal tissue 23
 - testing 8–11
- Caldicott report 44
- cardiovascular tissue, retrieval and processing 24
- CD34+ cells, enumerated, in HPC-C 38
- CD34 selected, definition 34
- cellular therapy products *see* HPCs
- central venous catheterization 32
- CFU-GM 38
- Clinical Pathology Accreditation (CPA)
 - accredited laboratories 8
- clonogenic assays 38
- Clostridium* sp. 18
- CMV, testing 37

- coercion or inducement to donate 6
- competence 6
- confidentiality *see* data protection
- consent
 - HPC discard 43
 - HPC donation 30, 31, 35
 - tissue donation 5, 6
- consultant anaesthetist 32
- cord blood *see* haemopoietic progenitor cells, cord blood (HPC-C)
- Cord Blood Bank, written agreements 32
- Coroner 6, 14
- cross-contamination, avoidance 18, 20, 36
- cryopreservation
 - of cardiovascular tissue 24
 - of HPCs 35–36
 - of tissues 19
- cryopreserved, definition 33

- data protection and confidentiality 1, 6, 30, 44
- delivery practices 32
- density enriched, definition 33
- Designated Individual
 - HPC collection facility 31
 - tissue establishment 1, 5, 6
- discard policy 20, 43
- distribution, of tissue 21, 24
- donation record, labelling 14
- donation sample 9
- donor lymphocyte infusions (DLI) 29
- donor samples, archiving 11
- Donor Selection Guidelines* 2, 6, 7, 8, 10, 28
- Donor Transplant Co-ordinator, referral 5
- donors
 - autologous 10–11, 30–31
 - data protection and confidentiality 1, 6, 30
 - deceased *see* cadaver donors
 - follow up 30
 - medical history and examination 7, 30–31
 - positive identification 9
 - referral 5
 - selection 5–12, 30–31
 - reference documents 28
 - testing 8–9, 30–31
 - tissue-specific considerations 8
 - see also* consent
- double container system 14

- ethylene oxide 18, 19
- EU Directive on In Vitro Diagnostic Medical Devices (98/79/EC) 8
- EU Directive on Tissues and Cells (2004/23/EC) 1, 27–28
- ex vivo expanded, definition 34

- FACT-JACIE Standards 27, 28, 29
- FBC, before apheresis 37
- follow up, for donors 10, 30
- freeze-drying 19

- gamma irradiation 18–19
- gene manipulated, definition 34
- glycerolization 19

- haemoglobinopathy 37
- haemopoietic progenitor cells (HPCs) 27–44
 - apheresis (HPC-A)
 - definition 33
 - donors 30, 32
 - archival samples 38
 - bacteriological/fungal screening 38
 - collection facilities 31–32
 - component definitions 32–34
 - cord blood (HPC-C)
 - collection identification procedures 32
 - definition 33
 - donors 31
 - written agreement 32
 - discard procedures 43
 - donors 30–31, 36–38
 - dose required 34
 - inventory control 35
 - labelling 35–36, 38–42
 - marrow (HPC-M)
 - definition 33
 - donors 30, 32
 - processing 34
 - processing facility 29
 - reference documents 1–2
 - release 43
 - repeat donations 31
 - storage 35–36
 - terminology 29
 - testing 36–38
 - thawing and infusion 43
 - third party donations 34
 - transportation 43
 - written request from transplant physician 34
- HBsAg 8, 36
- HBV testing 8, 37
 - cadaver donors 10
- HCV testing 8, 37
 - cadaver donors 10
- heart valves *see* cardiovascular tissue
- histocompatibility, reference 28
- HIV testing 8, 37
 - cadaver donors 10
- HLA typing 37–38
- human growth factors 32
- Human Tissue Act 2004 1, 6, 28
- Human Tissue Authority 1, 6
 - Codes of Practice 6, 28
- Human tissue (quality and safety for human application) regulations 2006 (draft) 28
- Human Tissue (Scotland) Act 2006 1, 6

- iliac crest, procurement from cadavers 23
- infant donor, deceased 10, 11
- infectious disease marker testing 36–37
- instruments, sterility 13
- inventory control, for HPCs 35

- JACIE Accreditation Manual 28

- labelling
 - of donation record 14
 - of HPCs 35–36, 38–42
 - of samples 14
 - of shipping container 21
 - of tissues 14, 20–21
- laboratories, accreditation/licensing 8

- malaria 36, 37
- marker organisms 18, 19
- marrow *see* haemopoietic progenitor cells, marrow (HPC-M)
- medical supervision and advice, availability 32
- Medicines and Healthcare Products Regulatory Agency (MHRA) licensed laboratories 8
- microbiological monitoring, of controlled work areas 18
- microbiological testing, for tissue donors 8–9

- NETCORD-FACT Standards 27, 28, 29
- nucleic acid amplification technique (NAT) testing 8, 9
- Nuffield Council of Bioethics guidance 6

- osteochondral allografts 23–24

- packaging, requirements 20–21
- patient records and results, requirements 44
- plasma & RBC reduced, definition 33
- plasma reduced, definition 33
- policies and procedures, requirements 29
- post quarantine sample 9
- pregnancy 37
- preservation methods 19
- Procurator Fiscal 6, 14
- product modifications, definitions 33–34
- progenitor cell mobilization 32
- purchased materials and solutions, inspection 13

- quality assurance 29

- RBC reduced, definition 33
- recall procedure 22, 30

- records, requirements 22, 44
- reference documents
 - for donor selection 28
 - for tissue banking and haemopoietic progenitor cells 1–2
- refrigeration devices, requirements 19–20
- release
 - of cord blood (HPC-C) 43
 - of tissue 11, 20
- resuscitation facilities 32
- retrieval times 14
- Rh D typing 9, 37, 38
- Rules and Guidance for Pharmaceutical Manufacturers and Distributors 2002* 15
- samples
 - archival 11, 38
 - identification and documentation 9
 - labelling 14
 - maternal 8, 9, 10, 11, 38
 - of skeletal tissue 23
- shipping container, labelling 21
- sickle cell 37
- skeletal tissue
 - from living donors 15
 - retrieval and processing 23–24
- skin
 - positive bacteriology or mycology 15
 - retrieval and processing 25
- solutions
 - inspection 13
 - requirements 19
- specialist advisors 5
- storage
 - of cardiovascular tissues 24
 - deep-frozen 15
 - of frozen skeletal tissues 23
 - of HPCs 35–36
 - preliminary 14
- syphilis, testing 8, 36, 37
- T cell depletion, definition 33
- terminal antimicrobial processing 15, 17
- terminal microbial processing 18
- thawing
 - of cardiovascular tissues 24
 - of haemopoietic progenitor cells (HPCs) 43
- therapeutic cells (TC)
 - definition 33
 - terminology 29
- third party referrals and agreements 5–6, 8, 13, 29
- tissue
 - accidental contamination 13
 - commercial use 6
 - discard procedures 20
 - double container system 14
 - labelling 14, 20–21
 - packaging for issue 20–21
 - pooling 19
 - preservation methods 19
 - processing, general guidelines 15
 - re-testing 11
 - release 11, 20
 - retrieval 14
 - storage 11, 19–21
 - temperature/time relationships 16, 23
 - tracking and traceability 5, 21–22
 - transportation 15
- tissue donors *see* donors
- tissue establishments
 - data protection and confidentiality 1
 - facilities 13
 - legislation and regulation 1–2
 - validation of processes and equipment 11
- toxoplasmosis 36
- transport solution, documentation 15
- transportation
 - of haemopoietic progenitor cells (HPCs) 43
 - of tissue 15
- tumour cell depletion, definition 34
- venous access 32
- World Marrow Donor Association (WMDA) Standards 28

