Guidelines for the Blood Transfusion Services

Chapter 22: Haemopoietic progenitor cells

http://www.transfusionguidelines.org/red-book/chapter-22-haemopoietic-progenitor-cells

Chapter 22:

Haemopoietic progenitor cells

22.1: Introduction

Cellular therapy is now covered by a variety of legislation. The EU Directive on Tissues and Cells (2004/23/EC) and its associated Commission Directives (2006/17/EC and 2006/86/EC) have been transposed into UK law as the Human Tissue (Quality and Safety for Human Application) Regulations, 2007 as amended. The Human Tissue Act 2004, Human Tissue (Scotland) Act 2006 and Directions or Codes of Practice issued by the Human Tissue Authority also apply. In addition, there are a number of key international standards for haemopoietic stem cells, notably the FACT-JACIE and the NetCord-FACT Standards and the WMDA standards. The lists of publications in sections 22.1.1 and 22.1.2 have been grouped according to their origins.

The guideline references in this chapter apply to the donation, collection, testing, processing, cryopreservation, storage and distribution of haemopoietic progenitor cells (HPC) and mononuclear cells (MNC) within the UK. These guidelines are applicable to stem cell donor registries and to bone marrow, peripheral blood and cord blood collection and processing facilities, and importing facilities, hereafter mentioned as establishments.

22.1.1: UK Regulation/Guidelines

1. Statutory Instrument 2007 No. 1523 The Human Tissue (Quality and Safety for Human Application) Regulations 2007, and subsequent amendments. Available at www.legislation.gov.uk
2. HTA Guide to Quality and Safety Assurance for Human Tissues and Cells for Patient Treatment (current edition), available at www.hta.gov.uk/guidance-professionals/regulated-sectors/human-application/hta-guide-quality-and-safety-assurance
3. Human Tissue Act 2004 (except Scotland). Available at www.legislation.gov.uk
4. Human Tissue (Scotland) Act 2006. Available at www.show.scot.nhs.uk
5. Human Tissue Authority Codes of Practice. Available at www.hta.gov.uk
    1. Guiding principles and the fundamental principle of consent (Code A)
    2. Donation of Allogeneic Bone Marrow and Peripheral Blood Stem Cells for Transplantation (Code G).
6. Human Tissue Authority Guidance document for establishments working with Umbilical cord blood. Available at www.hta.gov.uk/guidance-professionals/regulated-sectors/human-application/establishments-involved-cord-blood
7. Data Protection Act 2018. Available at www.gov.uk/data-protection
8. BSHI Guidelines for HLA matching and donor selection for haematopoietic progenitor cell transplantation. Available at www.bshi.org.uk

9. Joint UKBTS Professional Advisory Committee's (JPAC) Donor Selection Guidelines for either cord blood donors or bone marrow/peripheral blood stem cell donors. Available at www.transfusionguidelines.org
10. Joint UKBTS Professional Advisory Committee's (JPAC) Geographical Disease Risk Index (GDRI). Available at: www.transfusionguidelines.org
11. Advisory Committee on the Safety of Blood, Tissues and Organs (SaBTO) Microbiological Safety Guidelines. Available at www.gov.uk/government/publications/guidance-on-the-microbiological-safety-of-human-organs-tissues-and-cells-used-in-transplantation

22.1.2: European & International Directives/Guidelines

1. EDQM Guide to the quality and safety of tissues and cells for human application. Available at www.edqm.eu/en/guide-to-the-quality-and-safety-of-tissues-and-cells-for-human-application1
2. EC Guidelines to Good Manufacturing Practice (Eudralex) Manufacture of Sterile Medicinal Products. Available at ec.europa.eu/health/medicinal-products/eudralex_en
3. International Standards for Cellular Therapy Product Collection, Processing, and Administration. From the Foundation for the Accreditation of Cellular Therapy (FACT) and the Joint Accreditation Committee of ISCT-Europe and EBMT (JACIE). Available at www.ebmt.org/accreditation/jacie-standards
4. International Standards for Cellular Therapy Product Collection, Processing, and Administration Accreditation Manual. Available at www.jacie.org
5. NetCord-FACT International Standards for Cord Blood Collection, Banking and Release for Administration. Available at www.factwebsite.org
6. NetCord-FACT Cord Blood Accreditation Manual. Available at www.factweb.org/forms/store/CommercePlusFormPublic/search?action=Publications
7. World Marrow Donor Association (WMDA) International Standards for Unrelated Haematopoetic Stem Cell Donor Registries - promotes a range of standards, guidelines and recommendations to facilitate the exchange of haematopoietic stem cells across international borders. Available at www.wmda.info
8. European Federation for Immunogenetics (EFI) 'Standards for histocompatibility testing'. Available at efi-web.org
9. National Marrow Donor Program (USA) Standards. May be helpful in benchmarking for equivalent UK standards. Available at www.marrow.org
10. WMDA Donor Medical Suitability Recommendations. Available at share.wmda.info/display/DMSR/WMDA+Donor+Medical+Suitability+Recommendations+Main+page

22.2: Terminology

This chapter aligns with the terminology described at FACT-JACIE International Standards for Haemopoietic Cellular Therapy, Product Collection, Processing, and Administration, as below.

www.ebmt.org/accreditation/jacie-standards

22.3: Policy and procedure requirements and Safety

22.3.1: HTA licensing and requirements

The procurement and testing of human tissues or cells in UK should only be carried out by establishments holding an appropriate HTA licence or by individuals or organisations working under the authority of a third-party agreement with an establishment holding an appropriate HTA licence.

The below requirements apply to the establishments and third parties which carry out the procurement, testing, processing, distribution, or export of tissues and cells for human application, and for licensed establishments which store or import tissues and cells for human application.

www.hta.gov.uk/guidance-professionals/regulated-sectors/human-application/hta-guide-quality-and-safety-assurance

22.3.2: FACT-JACIE and NetCord-FACT standards

The FACT-JACIE and NetCord-FACT standards are available for the clinical and laboratory facilities who wish to conform to the FACT-JACIE and NetCord-FACT Standards as appropriate.

www.ebmt.org/accreditation/jacie-standards

22.4: Adverse events and reactions

22.4.1: HTA Guide for the management of serious adverse events (SAEs) and reactions (SARs)

All licensed establishments must have a system in place for reporting, investigating, registering and recording information about SAEs and SARs which may influence the quality and safety of tissues and cells, and which may be associated with any licensable activity, as well as any SAR observed during or after clinical application which may be linked to the quality and safety of tissues and cells.

www.hta.gov.uk/guidance-professionals/regulated-sectors/human-application/hta-guide-quality-and-safety-assurance

22.4.2: WMDA reporting system

WMDA maintains a voluntary central global reporting system to report Serious (Product) Events and Adverse Reactions – S(P)EARs as below

https://spear.wmda.info/

22.5: Donor selection, consent and testing

Establishments must have detailed policies and procedures for the testing and assessment of donors of stem cells. These must be in accordance with the requirements of the Human Tissue (Quality and Safety for Human Application) Regulations 2007 (as amended), UK-JPAC standards, FACT-JACIE Standards and the WMDA standards.

Anonymity must be maintained between donors and recipients in accordance with the requirements of EU Directive 2004/23/EC (Northern Ireland) and the UK information governance regulations.

www.transfusionguidelines.org/dsg/bm

share.wmda.info/display/DMSR/WMDA+Donor+Medical+Suitability+Recommendations+Main+page

www.ebmt.org/accreditation/jacie-standards

fact.policytech.com/dotNet/documents/?docid=534&public=true=

http://data.europa.eu/eli/dir/2004/23/oj

22.6: Collection, processing and storage

Stem Cells and Therapeutic Cells should only be collected in a hospital facility or Blood Service apheresis unit with appropriate experience (see section 5.8) and which meets the standards required by the Human Tissue (Quality and Safety for Human Application) Regulations 2007 (as amended), FACT-JACIE Standards and NetCord-FACT Standards as appropriate.

HTA Guide to Quality and Safety Assurance for Human Tissues and Cells for Patient Treatment
www.hta.gov.uk/guidance-professionals/regulated-sectors/human-application/hta-guide-quality-and-safety-assurance

FACT-JACIE Standards Parts CM, C and D
www.ebmt.org/accreditation/jacie-standards

22.7: Testing of haemopoietic progenitor cell donors and components

Infectious disease marker testing, ABO and RhD typing and clonogenic assays must be done in accordance with the HTA guide to quality and safety assurance for tissues and cells for patient treatments -updated on January 2021, and the SaBTO guidance.

Additional information and guidance available with FACT-JACIE, WMDA and NetCord-FACT standards.

The minimum current requirements for mandatory and additional microbiology testing (serology and/or NAT) are described in Chapter 9.

Annex 7 indicates the requirements for the timing of testing for each type of HPC.

22.8: Requirements for the timing of testing

Please see Annex 7 for guidance relating to the timing of testing for different categories of HPC.

22.9: Labelling, packaging, transportation and release

The mandatory requirements for these are described in the HTA's Guide to Quality and Safety Assurance for Human Tissue and Cells for Patient Treatment.

The FACT-JACIE Standards and NetCord-FACT Standards will also apply as appropriate.

The requirement for an EU Single European Code (SEC) still applies in Northern Ireland.

health.ec.europa.eu/blood-tissues-cells-and-organs/implementation/single-european-code-sec-tissues-and-cells_en#:~:text=The%20%22Single%20European%20Code%E2%80%9D%20or,type%20of%20tissue%20or%20cells

22.10: Disposal of haemopoietic progenitor cells

Disposal of cellular therapy products shall include the following requirements shall meet the EBMT guideline requiments (Chapter D12: Disposal)

www.ebmt.org/accreditation/jacie-standards

22.11: Record Maintenance

All patient records and results should be maintained to comply the requirements of the GDPR.

ico.org.uk/for-organisations/guide-to-data-protection/guide-to-the-general-data-protection-regulation-gdpr/accountability-and-governance/documentation

Establishments must comply with SaBTO advice in record keeping and maintenance.

www.gov.uk/government/publications/guidance-on-the-microbiological-safety-of-human-organs-tissues-and-cells-used-in-transplantation

The requirements for these are described in the Human Tissue (Quality and Safety for Human Application) Regulations 2007 (as amended), FACT-JACIE Standards, NetCord-FACT Standards and WMDA standards as above.

22.12: Labelling, packaging, transportation and temperature controls

The requirements for these are described in the HTA's Guide to Quality and Safety Assurance for Human Tissue and Cells for Patient Treatment, FACT-JACIE Standards and NetCord-FACT Standards and the requirements for labelling are summarised in Tables 22.2 and 22.3.

Table 22.2 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 concentration 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	

Red blood cell 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)	
Statement ‘Do not irradiate’				AT	AT	
Statement ‘Not for infusion’ including reason				AT (if applicable)	AT (if applicable)	
Name and address of receiving institution						AT
Name and telephone number of contact person at receiving institution						AT
Statement ‘Medical specimen’						AT
Statement ‘Do not X-ray’						AT

Name, address and telephone number of shipping facility						AT
AF = affixed, AT = attached or affixed, AC = accompanying or attached or affixed						

22.13: 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 standard operating procedures. Responsibility for setting policies for exceptional release and for issuing products on concession resides with the medical director/advisor.

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 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.

For cord blood donations release occurs at two stages:

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

Table 22.3 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 cord blood 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 and autologous HPC-C units)	AF	AF		AF	AF	

Collection centre identifier		AF	AT			
Date of collection		AF		AC	AC	
Time of collection		AC				
Name and volume or concentration of anticoagulant and other additives		AF		AC	AC	
Recommended storage temperature		AT		AF	AF	
Donor name (directed allogeneic and autologous HPC-C units)		AF		AF	AF	
Recipient’s name, unique identifier or family (directed allogeneic and 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 the end of processing				AC	AC	
Date of cryopreservation				AC	AC	
ABO group and Rh type				AC	AC	
HLA phenotype				AC	AC	
Number of nucleated cells post-processing				AC	AC	
Gender of HPC-C infant donor				AC	AC	
Identity of the cord blood bank				AF	AF	

Statement ‘Properly identify intended recipient and product’					AT	
Statement ‘For use by intended recipient only’ (allogeneic HPC-C units)					AT	
A statement indicating that leucoreduction filters should not be used					AT	
Statement ‘Do not irradiate’					AT	
Statement ‘For non-clinical use only’ (if applicable)					AT	
Biohazard labels – if applicable		AF	AF	AT	AT	
Date of distribution					AC	AF
Shipping facility name, address, telephone 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 = ccompanying or attached or affixed						

22.14: 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.

22.15: 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. 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.

22.16: Disposal of haemopoietic progenitor cells

- Appropriate prospective consent for discard should have been obtained. 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.
- 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.
- 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. The records for discarded components must indicate the component discarded, date of discard and method of disposal.
- The method of disposal and decontamination must meet the UK laws, current codes, rules and regulations for disposal of biohazardous materials.

22.17: Records

22.17.1: 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 shall be accurate, legible and indelible.
- 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 required for full traceability must be kept for a minimum of 30 years after clinical use, in an appropriate and readable storage medium.
- Records including raw data, such as original temperature monitoring records, which are critical to the safety and quality of the tissues and cells, must be kept for at least 10 years after any expiry date, clinical use or disposal of the tissues and cells.

22.17.2: Records to be maintained

The requirements for these are described in the EU Directives 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.

22.17.3: Records in cases of divided responsibility

If two 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.