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. For advanced therapy medicinal products there is EU Directive 2001/83/EC with its subsequent amendments and Regulation (EC) No. 1394/2007 on advanced therapy medicinal products. 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. The lists of publications in sections 22.1.1 to 22.1.5 have been grouped according to their origins.

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 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.

22.1.1: European Union Directives/guidelines


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


11. The European Medicines Agency Committee for Medicinal Products for Human Use (CHMP) prepares scientific guidelines, in consultation with the Competent Authorities of the EU member states, to help applicants prepare marketing-authorisation applications for medicinal products for human use. Guidelines are intended to provide a basis for practical harmonisation of the manner in which the EU member states and the Agency interpret and apply the detailed requirements for the demonstration of quality, safety and efficacy contained in the EU Directives. Available at www.ema.europa.eu/ema/index.jsp.

22.1.2: International Standards


16. World Marrow Donor Association (WMDA) promotes a range of standards, guidelines and recommendations to facilitate the exchange of haemopoietic stem cells across international borders. Available at www.worldmarrow.org.

22.1.3: Human Tissue Authority


22.1.4: Histocompatibility, donor selection and microbiology documents


24. Joint UKBTS/NIBSC Professional Advisory Committee’s (JPAC) Donor Selection Guidelines for either cord blood donors or bone marrow/peripheral blood stem cell donors are available at www.transfusionguidelines.org.uk.


22.1.5: UK legislation


22.2: 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 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).

22.3: Policy and procedure requirements

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. A risk management approach must be demonstrated.

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 maximise safety for both donors and recipients.

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.

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 recognised 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.

22.4: Safety requirements

Each HPC-processing facility must be operated in a manner to minimise risks to the health and safety of employees, donors and recipients. Suitable facilities and equipment must be available to maintain safe operations.

There must be procedures for microbiological, chemical and radiation safety, as appropriate, and a system for monitoring training and compliance.
HPC and TC collections must be handled and discarded with precautions that recognise the potential for exposure to infectious agents.

**22.5: Adverse events and reactions**

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.

These systems must also apply to any serious adverse events and reactions observed after administration of HPC components.

Documentation of these events shall be reviewed by the facilities’ directors as appropriate.

The Designated Individual must ensure that these events are notified to the HTA within 24 hours of discovery.

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.

**22.6: Donor selection, consent and testing**

**22.6.1: Allogeneic HPC-M donors**

**22.6.1.1: 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 Directives on Tissues and Cells, FACT-JACIE Standards and the WMDA.

- 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 possible need for second donations of HPC or TC; 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.

**22.6.1.2: Medical history, physical examination and testing**

- The donor medical assessment must be performed according to the requirements of the EU Directives on Tissues and Cells, FACT-JACIE Standards and the WMDA.

- Anonymity must be maintained between donors and recipients in accordance with the requirements of EU Directive 2004/23/EC. The British Bone Marrow Registry (BBMR) and the Welsh Bone Marrow
Donor Registry (WBMDR) must have robust policies for donor anonymity and follow-up in accordance with the requirements of the WMDA, FACT-JACIE and NetCord-FACT Standards and the relevant EU Directives.

22.6.2: Allogeneic HPC-A donors

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

The requirements of section 22.6.1 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 mobilise stem cells.

22.6.3: 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 22.9, 22.10 and 22.11.

22.6.4: 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 a 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.

22.6.5: 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 Directives on Tissues and Cells, NetCord-FACT Standards and the WMDA.

- Maternal assessment must be performed by appropriately trained staff, according to the requirements of the EU Directives on Tissues and Cells, NetCord-FACT Standards and the WMDA.

- Infant assessment must be performed by appropriately trained staff, according to the requirements of the EU Directives on Tissues and Cells, NetCord-FACT Standards, SaBTO and the WMDA.

- Testing requirements, see section 22.11 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 Directives on Tissues and Cells, NetCord-FACT Standards and the WMDA.

- 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, the EU Directives on Tissues and Cells and NetCord-FACT Standards.

22.7: Collection facilities for HPC-A, HPC-M, HPC-C and TC

22.7.1: 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 section 5.8) and which meets the standards required by the EU Directives 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 Directives 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 Designated Individual as defined by the EU Directives on Tissues and Cells/Human Tissue Act.

22.7.1.1: HPC-M donors
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.

22.7.1.2: HPC-A donors
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 mobilisation 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 catheterisation (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 catheterisation has been confirmed.
22.7.1.3: HPC-C collections

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.

22.8: Component definitions

22.8.1: 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.

**Investigational medicinal product (IMP)**: A pharmaceutical form of an active substance or placebo being tested or used as a reference in a clinical trial, including a product with a marketing authorisation when used or assembled in a way different from the authorised form, or when used for an unauthorised indication, or when used to gain further information about the authorised form. These products require a separate IMP manufacturer’s licence from the Medicines and Healthcare products Regulatory Agency (MHRA).

**Advanced therapy medicinal product (ATMP)**: An ATMP is a medicinal product which is:

- a gene therapy medicinal product as defined in Part IV of Annex 1 to Directive 2001/83/EC; or

- a somatic cell therapy medicinal product as defined in Part IV of Annex 1 to Directive 2001/83/EC; or

- a tissue engineered product as defined in Article 2 1 (b) of the ATMP Regulation.

The MHRA is the Competent Authority for the assessment of applications for clinical trial authorisations and the associated manufacturer’s licence for investigational ATMPs. It is also the Competent Authority for ATMPs which are prepared and used under the hospital exemption scheme (laid down in Article 3 (7) of the ATMP Regulation) and made and supplied under the ‘specials’ scheme.

22.8.2: 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 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

22.8.3: Product modifications

B cell depleted: Cells processed by negative selection for B 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.

CD34 selected: Enriched cells processed by positive selection for CD34 antigen bearing cells.

Cryopreserved: Cells frozen using devices, supplies and techniques validated to maintain viability.

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.

Ex vivo expanded: Cells that have been cultured in vitro for the purpose of producing and/or enriching for a specific functional subset. Note: Ex vivo expanded cells may require an IMP or ATMP manufacturer’s licence from the MHRA.

Gene manipulated: Cells that have been processed to alter their own genes or introduce new genetic material.
**Plasma and 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.

**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.

**RBC reduced:** Cells remaining after depletion of mature erythrocytes by sedimentation and/or centrifugation using devices, supplies and techniques validated for this purpose.

**T cell depleted:** Cells processed by negative selection for T lymphocytes.

**Tumour cell depleted:** Cells processed by negative selection for tumour cells.

### 22.9: Haemopoietic progenitor cell processing standards

#### 22.9.1: Personnel and facilities

Processing facilities must comply with the requirements of the EU Directives 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 Designated Individual as defined by the EU Directives 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.

#### 22.9.2: Procedures

- Before processing there should be a written request from the transplant physician. This is not required for unrelated cord blood collections.

- Processing should be performed according to written procedures and policies. All procedures must be validated prior to implementation. Aseptic techniques must be employed. Any deviation from such written procedures shall be documented and reviewed.

- Documented process simulation must be routinely undertaken to demonstrate that all processes are adequate and staff and facilities are fit for purpose.

- 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 (colony-forming unit – granulocyte /macrophage) 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 22.11.

22.10: Storage of cellular therapy products

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

It is recommended that donations with a nucleated cell concentration above 200 × 10⁹/L are diluted to less than 200 × 10⁹/L, preferably with autologous plasma. HPC-A donations must be placed at 4 ±2°C if they are for liquid storage and/or are not being processed immediately. It is recommended that the final concentration after addition of the cryoprotectant is less than 100 × 10⁹/L.

• transport if appropriate.

Where donations of known virology or bacteriology positive material are stored, appropriate risk assessments ensuring adequate controls are in place must be completed.

22.10.1: 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.

22.10.2: 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.

22.10.3: 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, and state the number of containers and vials and number issued, dates of issue and numbers of containers and vials remaining.

22.10.4: 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 Standards.

- 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. HPC donations are generally stored for named patients in low volumes using containers with a high surface area. To minimise the risk of transient warming events that may reduce viability and to maximise the time available to salvage donations should a storage device fail 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 recognised, 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 standardised manual procedure must be provided to ensure and document that adequate levels of liquid nitrogen are maintained.

### 22.11: Testing of haemopoietic progenitor cell donors and components including therapeutic cells

#### 22.11.1: Infectious disease marker testing

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

The minimum current requirements include testing for HIV, HTLV I/II, HBV, HCV and syphilis. Additional testing may be required in some cases, e.g. for malaria and toxoplasmosis. Table 22.1 indicates the requirements for the timing of testing for each type of HPC, while Chapter 9 contains further information on microbiology testing procedures.

### Table 22.1 Requirements for the timing of testing

<table>
<thead>
<tr>
<th>Test</th>
<th>Allo HPC-A/HPC-M/TC</th>
<th>Auto HPC-A/HPC-M</th>
<th>HPC-C donor mother</th>
<th>HPC-C</th>
</tr>
</thead>
<tbody>
<tr>
<td>ABO + RhD</td>
<td>Test at each donation</td>
<td>Test at first donation</td>
<td></td>
<td>Day 0 to Day +7</td>
</tr>
<tr>
<td>anti-HIV 1/2 antibody</td>
<td>Day –30 to Day 0</td>
<td>Day –30 to Day 0</td>
<td>Day –7 to Day +7</td>
<td>Prior to release</td>
</tr>
<tr>
<td>anti-HCV antibody</td>
<td>Day –30 to Day 0</td>
<td>Day –30 to Day 0</td>
<td>Day –7 to Day +7</td>
<td>Prior to release</td>
</tr>
<tr>
<td>anti-HTLV I/II/ (pooled) antibody</td>
<td>Day –30 to Day 0</td>
<td>Day –30 to Day 0</td>
<td>Day –7 to Day +7</td>
<td>Prior to release</td>
</tr>
<tr>
<td>HCV RNA (pooled)</td>
<td>Day –30 to Day 0</td>
<td>Day –30 to Day 0</td>
<td>Day –7 to Day +7</td>
<td>Prior to release</td>
</tr>
<tr>
<td>HBsAg</td>
<td>Day –30 to Day 0</td>
<td>Day –30 to Day 0</td>
<td>Day –7 to Day +7</td>
<td>Prior to release</td>
</tr>
<tr>
<td>Test</td>
<td>Day –30 to Day 0</td>
<td>Day –30 to Day 0</td>
<td>Day –7 to Day +7</td>
<td>Prior to release</td>
</tr>
<tr>
<td>-------------------------------</td>
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<td>------------------</td>
<td>------------------</td>
<td>------------------</td>
</tr>
<tr>
<td>anti-HBc antibody</td>
<td></td>
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<tr>
<td>CMV</td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>Pregnancy test</td>
<td>–7 days preconditioning</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Malaria</td>
<td>Where clinical indication</td>
<td>Where clinical indication</td>
<td>Where clinical indication. All mothers where there is risk</td>
<td>Prior to release</td>
</tr>
<tr>
<td>Haemoglobinopathy, i.e. sickle cell</td>
<td>Where clinical indication</td>
<td>Where clinical indication</td>
<td></td>
<td>Prior to release</td>
</tr>
<tr>
<td>Syphilis screen*</td>
<td>Day –30 to Day 0</td>
<td>Day –30 to Day 0</td>
<td>Day –7 to Day +7</td>
<td></td>
</tr>
<tr>
<td>Bacteriology testing</td>
<td>If manipulation</td>
<td>If manipulation</td>
<td></td>
<td>On final product</td>
</tr>
<tr>
<td>FBC</td>
<td>Before each apheresis procedure</td>
<td>Before each apheresis procedure</td>
<td></td>
<td>Pre and post process</td>
</tr>
</tbody>
</table>

* Confirmatory tests should be performed if screen positive

Additional tests must be undertaken for quarantined HPC-C products where a Day 180 repeat test has not been performed on the mother. The following tests should be performed on the mother’s initial sample 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 re-tested at the time of issue of donation for all current markers of infection including the latest generation of assays.

**22.11.2: HLA typing**
• At initial registration: HLA-A, -B, -DR type by a Clinical Pathology Accreditation (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 cord blood unit for transplantation a sample obtained from a contiguous HLA type or short tandem repeat (STR) can be performed according to NetCord-FACT Standards.

22.11.3: ABO and RhD 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.

22.11.4: 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-FACT Standards and progenitor cell assays should be assessed on a thawed sample before release of the unit for transplant.

22.11.5: 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.

22.11.6: Test samples
Archival samples must be stored for reference and any future testing that may be required as described in the EU Directives 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. Storage conditions must:

• maintain cell viability (below –150°C)
• be suitable to obtain material for the preparation of 50 mg DNA.
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

<table>
<thead>
<tr>
<th>Element</th>
<th>Partial label</th>
<th>Label at completion of collection</th>
<th>Label during processing</th>
<th>Label at completion of processing</th>
<th>Label at distribution</th>
<th>Inner and outer shipping container</th>
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<td>AF</td>
<td>AF</td>
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</tr>
<tr>
<td>Recipient name and identifier</td>
<td>AF (if applicable)</td>
<td>AF (if applicable)</td>
<td>AF (if applicable)</td>
<td>AF (if applicable)</td>
<td>AF (if applicable)</td>
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<td>Date, time collection ends and (if applicable) time zone</td>
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<td>Approximate volume</td>
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</tr>
<tr>
<td>Name and volume or concentration of anticoagulant and other additives</td>
<td>AC</td>
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<td>AC (if applicable)</td>
<td>AC (if applicable)</td>
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<td>Statement ‘Warning; this product may transmit infectious agents’</td>
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<td>Expiration time</td>
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<td>Statement ‘For autologous use only’ or Statement ‘For use by intended recipient only’</td>
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<td>AF (if applicable)</td>
<td>AF (if for allogeneic recipient)</td>
<td>AF (if for allogeneic recipient)</td>
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</tr>
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<td>Statement ‘Do not irradiate’</td>
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</tr>
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<td>Statement 'Not for infusion' including reason</td>
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<td>AT (if applicable)</td>
<td></td>
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</tr>
</tbody>
</table>
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
<table>
<thead>
<tr>
<th></th>
<th>Label at completion of collection</th>
<th>from collection</th>
<th>Label at completion of processing</th>
<th>unit release</th>
<th>Dry shipper labelling at issue</th>
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<td>Collection centre identifier</td>
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<td>Date of collection</td>
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<tr>
<td>Time of collection</td>
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<tr>
<td>Name and volume or concentration of anticoagulant and other additives</td>
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</tr>
<tr>
<td>Recommended storage temperature</td>
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<td>Volume or weight of the HPC-C unit at the end of collection</td>
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<td>Volume or weight of the HPC-C unit at the end of processing</td>
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<td>ABO group and Rh type</td>
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<td>Number of nucleated cells post-processing</td>
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<tr>
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<td>Statement ‘For use by intended recipient only’ (allogeneic HPC-C units)</td>
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<td>A statement indicating that leucoreduction filters should not be used</td>
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<tr>
<td>Statement ‘Do not irradiate’</td>
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</tr>
<tr>
<td>Statement ‘For non-clinical use only’ (if applicable)</td>
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<td>Biohazard labels – if applicable</td>
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<td>AF</td>
<td>AT</td>
<td>AT</td>
<td></td>
</tr>
</tbody>
</table>
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.