Guidelines for the Blood Transfusion Services

Chapter 21: Tissue banking: tissue retrieval and processing

http://www.transfusionguidelines.org/red-book/chapter-21

Chapter 21:

Tissue banking: tissue retrieval and processing

21.1: General considerations

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

All processes which affect the safety or quality of tissues must be validated.

21.1.1: Equipement - retrieval/processing

All equipment which affects the safety or quality of tissues must be validated.

Where possible single-use instruments must be used.

If it is impractical or not possible to use single-use instruments and reusable equipment has to be used, then the use must be risk assessed to ensure that all required mitigating actions are considered. Tissue Establishment reusable instruments and other items which come into direct contact with donor tissue during retrieval and processing must be thoroughly washed and sterilised between uses. These must be fully traceable to the individual tissue donor/batch and allow tracking through decontamination, sterilisation and use. These instruments should be washed and sterilised according to NHS Estates Health Technical Memoranda (HTM) 01-01,[1] 2030[2] and 2031[3] Instruments must not be allowed to dry out before washing prior to sterilisation. Prompt removal of residual blood and tissues is an important aspect of decontamination, particularly with regard to removal of prions.

21.1.2: Incoming materials and solutions

All purchased materials and solutions which could affect the tissue quality and safety must be inspected on receipt to ensure compliance with specification.

21.1.3: Use of third parties

UK Blood Transfusion Services Tissue Establishments may use third parties to perform tissue retrieval, (including eye 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. Tissue storage beyond 48 hours can only be undertaken at a premises directly licensed under the Q&S Regulations. Storage >48h cannot be undertaken at the premises of an unlicensed third party. 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 referenced from Chapter 19.

21.1.4: Tissue contamination

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

21.2: Retrieval

21.2.1: Retrieval times and preliminary storage

Tissue retrieval should be completed as soon after death as possible. For eye donation retrieval must be completed within 24 hours after death and the body should preferably be cooled or refrigerated. For all other tissues, if the body has not been cooled or refrigerated, procurement must be completed within 12 hours after death. If the body has been cooled or refrigerated within 6 hours of death, procurement should preferably start within 24 hours and must be completed within 48 hours of death. In this context, the term ‘cooled’ is used to reference situations where the body is not placed in an actively refrigerated location, but other attempts to reduce body temperature are employed. These may include for example application of sufficient amounts of wet ice to the body, use of a cooling blanket or (for neonatal donors) a cold cot, or the body being located in a cold location following death.

Tissues must be placed at a temperature of 0–10°C within 4 hours of retrieval. See tables 21.2 and 21.2 (section 21.4).

21.2.2: General considerations for tissue retrieval

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

The procurement facility must be suitable for procurement of tissues and must be risk assessed prior to commencement of tissue retrieval.

A local sterile field must be created using sterile drapes. An appropriate antibacterial 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 separate surface which is covered with a sterile drape. Where possible, single-use 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 minimise the number of people present during deceased tissue retrieval and to ensure that other activities, such as post-mortem examinations, are not proceeding in the same location 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.

21.2.3: Deceased donor 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.

21.2.4: Labelling of donations

At the time of donation, the container for each category of tissue (e.g. 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 retrieval site. Blood samples, and where relevant bacteriology 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 while still preserving anonymity where required.

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 Establishment.

21.3: Transportation conditions from retrieval site to Tissue Establishment

Transportation systems must be validated to show maintenance of the required storage temperature.

Transport solutions must be validated to preserve the required characteristics of the tissue to be transported.

External contamination and desiccation must be avoided.

The type, lot, manufacturer and the expiry date of the transport solution and components coming into contact with the tissue, such as the primary container, must be documented.

21.4: Bacteriostasis and disinfection

Storage conditions and expiration periods must be supported by validation. Historical data, experience and documented literature are acceptable as evidence of validation. Any new processing or significant changes to existing processing are subject to pre-authorisation by the HTA.

21.4.1: Tissue without terminal antimicrobial processing

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

- antibiotic disinfection
- an alternative disinfection method
- 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.

21.4.2: Tissue with 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 Tables 21.1 and 21.2.

Table 21.1 Temperature/time relationships for banked tissues from living donors

Retrieved tissue	Must be placed at a temperature of between 0–10°C within 4 hours of retrieval.[1]
Bacteriostasis	Freezing tissue to –20°C or colder within 24 hours of retrieval can be used as a bacteriostatic treatment. Bone from living donors which is not frozen until 24–48 hours after retrieval must be subjected to terminal antimicrobial processing.
Long-term storage	Bone from living donors may be stored at –20°C or colder for up to 6 months or at –40°C or colder for up to 5 years. Temporary storage of frozen living donor bone between –20°C and –40°C is limited to 6 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 5 years from donation. Amnion preserved in low-concentration (50%) glycerol may be stored at –40°C or colder for up to 2 years.
Transportation and local storage	Must be transported and stored locally prior to clinical use, at –20°C or colder in order to have the designated expiry (specified above).

[1] As the tissue itself it taken directly from a living individual, setting temperature criteria for the tissue itself during this initial storage and transport is not feasible, therefore only the ambient temperature it must be kept at is specified.

Table 21. 2 Temperature/time relationships for banked tissues from deceased donors

Retrieval	For eyes, retrieval must be completed within 24 hours after death and the body should preferably be refrigerated For all other tissues, if the body has not been refrigerated, procurement of tissues must be completed within 12 hours after death. If the body has been refrigerated within 6 hours of death procurement should preferably start within 24 hours and must be completed within 48 hours of death.
Retrieved tissue	Must be placed at a temperature of between 0–10°C within 4 hours of retrieval.[1]
Bacteriostasis	Freezing tissue to a temperature of –20°C or colder within 24 hours of retrieval (or up to a maximum of 72 hours of death) can be used as a bacteriostatic treatment.
Long-term storage	**Frozen* tissue may be stored:** 1. At –20°C or colder for up to 6 months. 2. At –40°C or colder for up to 5 years. Temporary storage of frozen musculoskeletal tissue between –20°C and –40°C is limited to 6 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 5 years from donation. **Cryopreserved** tissue:** At –135°C or colder 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 5-year expiry. **Glycerol-preserved tissue:** Skin preserved in high-concentration (>90%) glycerol may be stored at between 0–10°C for up to 2 years. **Freeze dried tissue:** Freeze-dried tissue may be stored at ambient temperature for up to 5 years. This includes freeze dried demineralised bone tissue mixed with a glycerol carrier **Decellularised Tissue:** Decellularised dermis tissue that has been terminally sterilised may be stored at colder than –40° C for up to five years, or at up to +40°C for up to two years.
Transportation and local storage	**Frozen* tissues** must be transported and stored locally prior to clinical use, at colder than –40°C if they are to retain their original expiry date. If they are stored locally at temperatures colder than –20°C or warmer than –40°C, the expiry date must be reduced to a maximum of 6 months or the balance of the original expiry date, whichever is lower. **Cryopreserved** tissues** may be transported in the vapour phase of liquid nitrogen (–135°C or colder) or on dry ice (–79°C or colder). If tissues are transported on dry ice they should continue to be stored locally at –80°C or colder for a maximum of 6 months.

For the purposes of this guidance, the following definitions apply:

* Frozen tissue – Tissue stored at sub-zero temperatures, with ot without cryoprotectant.

** Cryopreserved tissue – Tissue preserved and stored at sub-zero temperatures using a cryoprotectant, either by controlled slow freezing or by vitrification.

[1] As the tissue itself it taken directly from a living individual, setting temperature criteria for the tissue itself during this initial storage and transport period is not feasible, therefore only the ambient temperature it must be kept at is specified.

21.4.3: 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 provided that a validated antimicrobial processing technique is used.

21.5: General guidelines for tissue processing

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

21.5.1: Aseptic processing facilities

Facilities for aseptic processing must comply with the *Rules and Guidance for Pharmaceutical Manufacturers and Distributors 2015*[5], EC Guidelines to Good Manufacturing Practice[6] and the Human Tissue (Quality and Safety for Human Application) Regulations 2007 (as amended)[7]. 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 sanitised
- 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)
- 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 authorised personnel
- documented system for general staff hygiene practices.

21.5.2: 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 are exposed to the environment, must have an air quality of Grade A and should have a Grade B background. (For further information see *Rules and Guidance for Pharmaceutical Manufacturers and Distributors 2015*[5] and the EC Guidelines to Good Manufacturing Practice.[6]) Any lowering of this standard in the background environment must be documented and it must be 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.

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.

Procedures must ensure that no cross-contamination between batches of tissue from different donors 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 retained.

21.5.3: 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 in the vicinity of exposed tissue.

Terminal antimicrobial processing must follow the filling of the final container. The procurement, processing and filling environment must be of sufficient quality to minimise 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.

21.5.3.1: Terminal sterilisation

Sterilisation is a statistical phenomenon, expressed as the probability of microorganisms surviving the procedure. The sterility assurance level (SAL) is the probability of a microorganism on one item within a batch or within a defined population. The accepted level for considering medical devices to be ‘sterile’ is a SAL of 10^{-6} (i.e. less than one item per million items will have a surviving microorganism on it). For medical devices, the microorganisms under consideration are contaminants (i.e. bacteria and fungi and their spores). Unless specifically stated, viruses are not routinely considered.

Because of the large numbers involved, demonstrating SAL of 10^{-6} must use procedures that extrapolate from smaller batches. For sterilisation procedures that show a log10/linear decrease in microbial viability, extrapolation can be achieved using the D-value (decimal reduction value) concept.

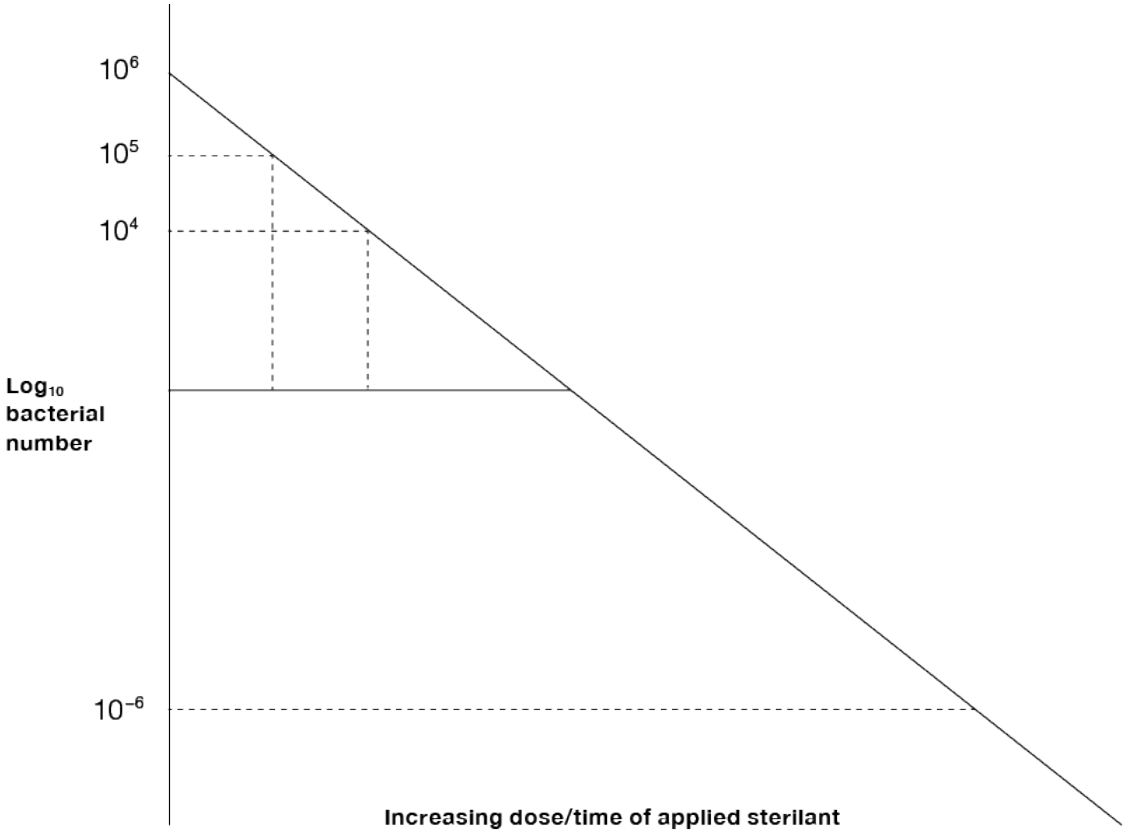

Figure 21.1 An example of increasing inactivation of bacteria related to increasing the dose of the sterilant

In the example shown in Figure 21.1, each log reduction requires an additional unit of the sterilant to be applied, hence D-value = 1.0. Therefore moving from an initial bioburden of 106 bacteria to a SAL of 10^{-6} would require 12 × D-value of the sterilant.

In practice, the processing that is applied to tissue grafts prior to application of the terminal sterilisation step often reduces the bioburden to close to zero. Therefore application of a sterilisation procedure sufficient to provide a 6-log reduction of bacteria is often satisfactory to achieve a SAL of 10^{-6}.

Very often, validation studies will be carried out using the microorganism that is known to be most resistant to the sterilisation procedure (often bacterial spores). This is therefore a 'worst-case' validation. Achieving a SAL of 10^{-6} for this microorganism will guarantee a significant overkill for more sensitive microbes.

21.5.3.2: Validation of terminal sterilisation

Whenever a novel terminal sterilisation step is introduced the following validations need to be addressed:

- That the sterilisation technique achieves a SAL of 10^{-6} for the most resistant microorganisms.
- That the sterilisation technique can be applied to the tissue graft in its final packaging without subsequent exposure, and that the integrity of the packaging is not adversely affected by the process.

- That the sterilisation technique does not adversely affect the essential properties of the graft and does not leave toxic residuals.
- That the sterilisation technique inactivates all categories of microorganisms commonly found on tissue grafts including vegetative Gram positive and Gram negative bacteria, vegetative fungi, and bacterial and fungal spores. This must be demonstrated either by literature review or validation.

21.5.4: 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.

21.5.5: Pooling

Pooling of tissues from different donors is not recommended and should only be considered if this is the only way in which clinical efficacy can be achieved.

21.5.6: Preservation methods

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

21.5.6.1: Freezing

For the purposes of this guidance this term applies to tissues that are frozen and stored under conditions that are unlikely to be compatible with preservation of cells. Frozen tissue must be stored below –20°C and the length of storage permitted depends on the temperature the tissues are stored at (see Tables 21.1 and 21.2).

21.5.6.2: Cryopreservation

For the purposes of this guidance this term applies to tissues that are treated with a cryoprotectant and/or cooled at a controlled rate in order to preserve cells. Cryopreserved tissue must be stored below –135°C. For storage at higher temperatures, validation must be performed to demonstrate that the required properties of the graft are maintained for the stated expiry.

21.5.6.3: Freeze-drying

Where tissues are freeze-dried, a sample of each type of tissue from each freeze-drying run must be analysed for residual water which must be less than 5% (weight/weight) of the dry weight of the graft or residual water activity of between 0 and 0.5 Aw.

21.5.6.4: Glycerolisation

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 an acceptable range within the tissue.

21.5.7: 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 and fully identified in the associated records.

21.6: 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. Material should be stored in the vapour phase of liquid nitrogen, not immersed in the liquid phase. Liquid nitrogen storage vessels should be designed to incorporate automatic filling systems to avoid transfer of filling hoses between vessels. Thermocouple temperature probes should be placed in storage vessels, with at least one probe located in the warmest position, as determined by temperature mapping.

Frozen and cryopreserved 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 in liquid nitrogen vessels because of the high levels of accumulated microbial contaminants found within these vessels.

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

21.6.1: 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 standard operating procedures. Responsibilities for setting policies for exceptional release of tissues reside with the authorised medical officer.

21.6.2: 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. Traceability records must be retained in the same way as for tissue used in human application.

21.6.3: 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 (tissue type, batch and shipment number if applicable), expiry date and supplying Tissue Establishment, 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, if applicable
- antimicrobial processing procedure used (if applicable)
- preservative and any other additives used and their concentration (if applicable)
- special instructions (e.g. ‘Do not freeze’), thawing, dilution instructions
- presence of known sensitising substances
- type of antibiotics added during processing (if applicable)
- any other potential residual processing agent
- RhD 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
- 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 sterilised after leaving the Tissue Establishment
- 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.
- in the case of autologous donations, the label must state ‘for autologous use only’
- in the case of directed donations, the label must identify the intended recipient.

21.6.4: 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:

- identification of the originating Tissue Establishment, including an address and telephone number and a contact person in the event of problems
- identification of the organisation responsible for human application of destination, including address and telephone number and the person to be contacted to take delivery of the container
- a statement that the package contains human tissue/cells and HANDLE WITH CARE
- 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’
- recommended transport conditions (e.g. keep cold, in upright position etc)
- safety instructions/method of cooling (when applicable)
- The date and time that the product was prepared for transportation
- in the case of autologous donors, the following indication: ‘FOR AUTOLOGOUS USE ONLY’
- Specifications concerning storage conditions (such as DO NOT FREEZE).

21.6.5: Distribution

All reasonable efforts must be made to ensure that tissues are sent to qualified individuals/organisations who have accepted responsibility for their proper handling and use. A written agreement must be in place between the Tissue Establishment and the organisation ordering the tissue.

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. Consideration should be given to the potential for extremes of external temperature during transportation.

21.6.6: Relevant Material and Storage Licenses

The Human Tissue Act defines ‘Relevant Material’ as: “material, other than gametes, which consists of or includes human cells.” Tissue Establishments must determine for each type of graft they prepare, and the processing applied, whether or not a graft type is classified as Relevant Material. If so, the Tissue Establishment must hold a Human Tissue Authority storage licence if it holds the tissue for more than 48

hours. Tissue Establishments should inform hospitals if a graft is classified as Relevant Material, and ensure that the hospital has an appropriate storage licence if they intend to hold the graft for more than 48 hours.

21.7: 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 21.3.

Table 21.3 Minimum donor/recipient data set to be kept

A. BY TISSUE ESTABLISHMENTS
Donor identification
Donation identification that will include at least: • Identification of the procurement organisation or Tissue Establishment • Unique donation identification number • Date of procurement • Place of procurement • Type of donation (e.g. single or multi-tissue; autologous or allogeneic; living or deceased).
Product identification that will include at least: • Identification of the Tissue Establishment • Type of tissue and cell/product (basic nomenclature) • Batch 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

- Identification of the supplier Tissue Establishment
- Identification of the clinician or end user/facility
- Type of tissues and cells
- Product identification
- Identification of the recipient
- Date of application
- Where applicable, date and method of disposal

21.8: Notification of serious adverse events and reactions

Tissue Establishments in the UK are required to report serious adverse events and reactions to the Human Tissue Authority (HTA), within 24 hours of the incident being identified, through the Serious Adverse Events and Reactions system. For the purposes of reporting, a serious adverse reaction (SAR) is defined as an unintended response, including a communicable disease, in the donor or in the recipient associated with the procurement or human application of tissues and cells that is fatal, life-threatening, disabling or incapacitating or which results in, or prolongs, hospitalisation or morbidity. A serious adverse event (SAE) is defined as any untoward occurrence associated with the procurement, testing, processing, storage and distribution of tissues and cells that might lead to the transmission of a communicable disease, to death or life-threatening, disabling or incapacitating conditions for patients or which might result in, or prolong, hospitalisation or morbidity.

Tissue Establishments shall ensure that there is a system in place to report, investigate, register and transmit information about serious adverse events and reactions. 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.

21.9: Additional guidelines for skeletal tissue retrieval and processing

21.9.1: 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 Establishment, these staff must follow a protocol provided by the Tissue Establishment in accordance with third party agreements. The removed bone should be placed, as quickly as possible, and whilst in the surgical field, in a sterile container and labelled in a manner to distinguish it from bone authorised for transplant.

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. Details of consumables and reagents coming in direct contact with the procured bone must be recorded (this does not include any items used during the elective surgery).

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 Establishment. Bone sampling must be carried out immediately prior to placing in the 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.

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

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

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 1 month of sampling and any handling or storage of the sample prior to testing must be aligned with the test kit manufacturer's recommendations or suitably validated. Please see Chapters 9 and 20 for further details. Note: If tissues are stored by a hospital for more than 48 hours then the hospital requires to be licensed by the HTA, as storage cannot be covered by a 'third party agreement'.

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 subjected to terminal sterilisation, e.g. gamma irradiation (>1.5 megarads = >15 kGy) (see section 21.5.4).

21.9.2: Procurement of skeletal tissues from deceased donors

If iliac crest is to be retrieved, it should be taken last in case the bowel is perforated and should be 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.

21.9.3: Processing of skeletal tissues

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

Cryopreservation of allografts must begin within 48 hours of procurement. These allografts must not be exposed to gamma irradiation and must therefore be procured and processed aseptically.

21.10: Cardiovascular tissue retrieval and processing

21.10.1: General

This section predominantly relates to the banking of heart valves.

21.10.2: Sizing and evaluation of cardiovascular tissue

Aortic and pulmonary valves should be sized at the annulus and the internal diameter recorded in millimetres. The competency of the valves should be evaluated.

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

For pulmonary patch allografts, the length and width of the graft 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. It may also be helpful to take a retain photographic records of the grafts.

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.

21.10.3: 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 Tissue Establishment should develop a list of exclusion criteria based on type and/or number of contaminating organisms prior to and following decontamination.

21.10.4: Cryopreservation

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

21.10.5: Storage and warming of cardiovascular tissues

For material stored at –135°C or below, if during warming the tissue is warmed too rapidly between the storage temperature and –100°C, fractures can occur. A validated method of warming (e.g. on dry ice) must be used to minimise 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 6 months will pertain.

21.10.6: 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.

21.11: Skin retrieval and processing

21.11.1: Skin retrieval

Skin sites should be shaved if necessary and treated with an antimicrobial agent such as chlorhexidine.

21.11.2: Skin processing

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

Samples of skin must be cultured for aerobic and anaerobic bacteria and fungi prior to and following decontamination. The tissue establishment’s microbiology policy should specify how these tests impact on suitability for clinical application.

21.12: Ocular tissue retrieval, processing and storage

21.12.1: Eye retrieval

All required documentation must be fully completed by the eye retriever, including information related to the tissue donor and body map.

Approved SOPs must be followed.

The final cosmetic appearance is of critical importance as family or friends may wish to view the body. Any bleeding or bruising resulting from the enucleation must be documented, and this documentation transferred to the tissue establishment.

21.12.2: Ocular tissue processing and storage

Corneas should be excised and placed in an appropriate storage solution as soon as possible, but no longer than 24 hours after enucleation. Corneas may be stored for up to 2 weeks at 4°C in an appropriate hypothermic storage solution. Alternatively, the great majority of corneas in the UK are stored for up to 4 weeks in organ culture at 34°C. The corneal endothelium is examined by light microscopy a few days before use to ensure its suitability for transplantation in patients with corneal endothelial disease/deficiency. Organ-cultured corneas are delivered to hospitals in medium containing 5% dextran to reverse the stromal oedema that occurs during storage. Corneas with an inadequate endothelium may still be suitable for anterior lamellar grafts. These corneas may also be transferred to 70% ethanol and stored at room temperature for up to 12 months for use in glaucoma surgery. Sclera, which is also stored in 70% ethanol for up to 12 months, is used for glaucoma or other reconstructive surgery. Ocular surface stem cells may be isolated from the limbus and expanded in ex vivo culture for treating limbal stem cell deficiency.

21.13: References

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