Site visit inspection report on compliance with HTA minimum standards

Great Ormond Street Hospital

HTA licensing number 11026

Licensed for the

- **procurement, processing, testing, storage and distribution of human tissues and cells for human application under the Human Tissue (Quality and Safety for Human Application) Regulations 2007 (as amended); and**
- **storage of relevant material which has come from a human body for use for a scheduled purpose**

23 and 24 May 2018

Summary of inspection findings

The HTA found the Designated Individual and the Licence Holder to be suitable in accordance with the requirements of the legislation.

Although the HTA found that Great Ormond Street Hospital (the establishment) had met the majority of the HTA standards, two major and eight minor shortfalls were found in relation to documented procedures, written agreements, regular evaluation of processes, risk assessments and environmental controls.

Particular examples of strengths and good practice are included in the concluding comments section of the report.

The HTA's regulatory requirements

The HTA must assure itself that the Designated Individual, Licence Holder, premises and practices are suitable.

The statutory duties of the Designated Individual are set down in Section 18 of the Human Tissue Act 2004. They are to secure that:

- the other persons to whom the licence applies are suitable persons to participate in the carrying-on of the licensed activity;

- suitable practices are used in the course of carrying on that activity; and
- the conditions of the licence are complied with.

The HTA developed its licensing standards with input from its stakeholders. They are designed to ensure the safe and ethical use of human tissue and the dignified and respectful treatment of the deceased. The HTA inspects the establishments it licences against four groups of standards:

- consent
- governance and quality systems
- premises facilities and equipment
- disposal.

This is an exception-based report: only those standards that have been assessed as not met are included. Where the HTA determines that a standard is not met, the level of the shortfall is classified as 'Critical', 'Major' or 'Minor' (see Appendix 2: Classification of the level of shortfall). Where HTA standards are fully met, but the HTA has identified an area of practice that could be further improved, advice is given to the DI.

Reports of HTA inspections carried out from 1 November 2010 are published on the HTA's website.

Licensable activities carried out by the establishment

'E' = Establishment is licensed to carry out this activity.

'TPA' = Third party agreement; the establishment is licensed for this activity but another establishment (unlicensed) carries out the activity on their behalf.

Tissue Category; Tissue Type	Procurement	Processing	Testing	Storage	Distribution	Import	Export
Progenitor Cell, Haematopoietic, PBSC; PBSC	**E**	**E**	**E/TPA**	**E**	**E**		
Progenitor Cell, Haematopoietic, Bone Marrow; Bone Marrow	**E**	**E**	**E/TPA**	**E**	**E**		
Progenitor Cell, Haematopoietic, Cord Blood; Cord Blood		**E**	**E/TPA**				
Progenitor Cell, Haematopoietic, Unspecified; PBMC	**E**		**E/TPA**				
Mature Cell, T Cell (DLI); DLI	**E**	**E**	**E/TPA**	**E**	**E**		
Other; Thymus	**E**	**E**	**E/TPA**	**E**			

Background to the establishment and description of inspection activities undertaken

This report refers to the activities carried out under the authority of the licence held by Great Ormond Street Hospital (GOSH). The establishment is licensed for the procurement, testing, processing, storage and distribution of human tissues and cells under the Human Tissue (Quality and Safety for Human Application) Regulations 2007. It is also licensed for the storage of relevant material which has come from a human body for use for a scheduled purpose under the Human Tissue Act 2004. The establishment has no material currently stored for research.

The establishment procures tissues and cells from paediatric patients for autologous and allogeneic (sibling donor) transplant, including peripheral blood stem cells (PBSCs); bone marrow (BM); donor lymphocyte infusions (DLIs), and; thymus gland tissue. Procurement of paediatric PBSC is carried out at GOSH by staff employed by another HTA-licensed establishment under the terms of an SLA. The establishment also receives units of umbilical cord blood and DLIs for transplant from HTA-licensed public registries under service level agreements, and from overseas registries.

For units procured on site, donor selection and consent is carried out by GOSH consultants. Donor serology and nucleic acid testing is carried out in the Microbiology / Virology Laboratory at GOSH which has UKAS accreditation.

All tissues and cells are receipted into the Cellular Therapy Unit (CTL) at GOSH before issue, processing and storage as appropriate. CTL staff check labelling and accompanying documentation for all tissues and cells including a check that mandatory biological tests have been carried out in the 30 days prior to the collection procedure. Any processing requests are recorded on a booking spread sheet before the cells arrive.

Processing in the CTL takes place in a clean laboratory that contains two laminar air flow cabinets capable of maintaining a grade A processing environment against a background of grade B. Access to the clean laboratory is via separate change rooms and material is moved into the clean laboratory via separate in/out hatches from a general laboratory area. Tissues and cells are brought into the laboratory for a number of processes including volume reduction and / or red cell depletion of bone marrow or PBSC harvests, washing of cryopreserved cord blood units, selection of CD34 enriched stem cells, reduction of TCRαβ/CD19 stem cells, cryopreservation of stem cells and thymus culture. The facility performs total nucleated cell count, CD3, CD34 and CD45 immunophenotype, and cell viability assays for each PBSC collection. In addition, colony-forming unit granulocyte-macrophage (CFU-GM) assays are carried out on in every fifth cryopreserved stem cell unit that is processed, and on cells identified for disposal after five years storage, to ensure sufficient cell recoveries. Engraftment data is continually monitored and discussed at regular quality meetings attended by the Designated Individual (DI).

Environmental monitoring (EM) of the clean laboratory is carried out during each processing session, including settle plates and particle monitoring in the cabinets, settle plates in the grade B area and finger dabs for processing staff. Weekly and monthly EM is also performed. The former includes settle plates and particle monitoring inside the cabinet and in grade B area and contact plates at set locations including the floor and hatches, whilst the latter includes active air sampling carried out by QA pharmacists. EM data is put onto spread sheets and trended. Results are discussed at quarterly Quality Management Meetings.

Cryopreservation of products and pilot samples takes place in a dedicated -80°C freezer with dimethyl sulphoxide/human serum albumin as the cryoprotectant. Three members of staff take part in the cryopreservation process to minimise the time between the addition of cryprotectant and freezing. Following cryopreservation, products and pilot samples are stored in one of two cryovessels. An additional quarantine cryovessel is used to store serologically positive samples or those pending receipt of serology results.

All storage containers, including cryovessels, freezers and refrigerators, are linked to a continuous temperature-monitoring unit, which feeds into a callout system via the Security department. Temperature excursions outside the set ranges trigger both audible alarms and the callout system and the system is tested regularly. The cryovesssels have an additional second probe linked to the callout procedure as a back-up. There are fixed oxygen depletion monitors linked to an alarm system in the liquid nitrogen storage area and staff carry portable monitors.

This report describes the routine site visit inspection of GOSH, which took place on 23 and 24 May 2018. A visual inspection of the areas of the premises where licensable activities take place was conducted; this included the paediatric apheresis area, theatres where bone marrow procurement takes place and the CTL

The inspection included discussions with key members of staff involved in the carrying out of licensable activities, including a Consultant Paediatric Haematologist, who is also the Designated Individual (DI), the Director for Cell Therapy, the Quality Manager for the CTL, and the Apheresis Lead Nurse.

Several roundtable discussions took place covering the management of the procurement and processing of thymus tissue, procurement and testing of material for clinical trials and the Quality Management System (QMS).

For the QMS, establishment staff gave an overview of the audits carried out within the establishment including an independent audit against all HTA standards by another HTA-licensed establishment. A review of incidents was carried out and three were selected for closer examination including the investigations carried out and corrective and preventative action (CAPA) plans.

An audit of the records associated with four samples processed and tested by the establishment was performed. Donor files were reviewed to ensure that they contained all relevant documentation, including consent forms, apheresis worksheets, serology test results, request to process forms, microbiology results, transportation records, processing records, an incident report form and a stem cell infusion report as appropriate. A check was also made against computerised records for one of the files focusing on traceability, cell counts, virology screening and EM results.

Inspection findings

The HTA found the Designated Individual and the Licence Holder to be suitable in accordance with the requirements of the legislation.

Compliance with HTA standards

Human Tissue (Quality and Safety for Human Application) Regulations 2007 Standards

Governance and Quality

Standard	Inspection findings	Level of shortfall
GQ1 All aspects of the establishment's work are supported by ratified documented policies and procedures as part of the overall governance process.		
b) There are procedures for all licensable activities that ensure integrity of tissue and / or cells and minimise the risk of contamination.	Written procedures are not sufficiently detailed to ensure consistency. The standard operating procedure (SOP) that describes EM does not describe the placement of settle plates within the cabinet, the use of second settle plates for processing that takes longer than four hours or the correct forms for settle plate location In addition, the monitoring of the general laboratory area in terms of particles is not clear. The SOP that describes the cryopreservation process does not contain any limits for time between the addition of DMSO and freezing, does not describe the use of the -80°C freezer in enough detail with relation to overwrapping of cassettes, internal shelf set-up of the freezer, the requirement to freeze only one unit at a time and for the freezer to remain undisturbed during the cryopreservation process. The contingency SOP does not describe the availability of an alternative -80°C freezer for cryopreservation. ***The establishment took action to address this shortfall before the issue of the final report. The HTA now assess this standard as fully met.***	**Minor**

d) There is a document control system to ensure that changes to documents are reviewed, approved, dated and documented by an authorised person and only current documents are in use.	The establishment's document control procedure allows for the addition of up to ten minor amendments as physical amendments to the hard copy of the SOP. The establishment maintains two hard copies of the SOPs and currently minor changes are added only to the hard copy stored in the office and not the working copy. This means there is a risk that the amendment will not be followed. Examples of minor amendments viewed by the inspection team concerned the addition of a step to minimise time between the addition of DMSO and freezing for the cryopreservation of stem cells and a change to the storage location of reagents. Changes such as these should be re-classified as major since they have the potential to impact on the integrity of the cells.	**Minor**
p) There are written agreements with third parties whenever an activity takes place that has the potential to influence the quality and safety of human tissues and / or cells.	There are no written agreements with laboratories that carry out confirmatory tests for virology or for tests that are not currently provided by the laboratory that is used for routine testing	**Minor**
GQ2 There is a documented system of quality management and audit.		
d) Processes affecting the quality and safety of tissues and / or cells are validated and undergo regular evaluation to ensure they continue to achieve the intended results.	Passive freezing was introduced over four years ago. The establishment does not monitor the rate of freezing for each cryopreserved sample. There are no plans in place to regularly re-evaluate the cryopreservation step to ensure that the freezing rate remains as expected. In April 2017, a validation of the freezing rate in a newly acquired -80°C was carried out and identified that the freezing rate of the smallest cryobags was higher than the set limit. This led to a change in working practices and the addition of an extra overwrap for this size of bag. During the validation no consideration was given to the fact that a slower freezing rate can be detrimental to cells. A lower limit was not set or assessed for any of the cryobags.	**Major**

GQ7 There are systems to ensure that all adverse events are investigated promptly.		
a) There are procedures for the identification, reporting, investigation and recording of adverse events and reactions, including documentation of any corrective or preventative actions.	The establishment has not outlined the procedures for SAEARs reporting for Virology or for tissues and cells distributed to end-users outside of GOSH.	**Minor**
GQ8 Risk assessments of the establishment's practices and processes are completed regularly and are recorded and monitored appropriately.		
a) There are documented risk assessments for all practices and processes.	Risk assessments have not been documented for all practices and processes.	**Major**
b) Risk assessments are reviewed regularly, as a minimum annually or when any changes are made that may affect the quality and safety of tissues and cells.	Risk assessments are not reviewed annually. ***The establishment took action to address this shortfall before the issue of the final report. The HTA now assess this standard as fully met.***	
d) A documented risk assessment is carried out to decide the fate of any tissue and / or cells stored prior to the introduction of a new donor selection criteria or a new processing step, which enhances the quality and safety of tissue and / or cells.	A risk assessment was not carried out for cryopreserved units that had already been stored at GOSH prior to the validation of a new -80°C freezer that showed a faster rate of freezing for the small volume cryobags.	

Premises, Facilities and Equipment

Standard	Inspection findings	Level of shortfall
PFE2 Environmental controls are in place to avoid potential contamination		
b) Where processing of tissues and / or cells involves exposure to the environment, it occurs in an appropriate, monitored environment as required by Directions 002/2018	The establishment's clean room has hatches that open into a general laboratory area. The grade of this room is unclear and there is no risk assessment of the impact of this on the grade B environment. Items passed through to the clean room routinely touch the sides of the hatches. Swabs are not taken to check that the cleaning of the hatches is effective. The establishment's regime for the incubation of settle plates used for monitoring the processing environment is not in line with recommendations of the European Directorate for the Quality of Medicines. The protocol risks not detecting microorganisms of both bacteria and fungi origin. The establishment did not have a risk assessment or evidence-based rationale for this alternate incubation protocol.	**Minor**

PFE3 There are appropriate facilities for the storage of bodies, body parts, tissues, cells, consumables and records.		
a) Tissues, cells, consumables and records are stored in secure environments and precautions are taken to minimise risk of damage, theft or contamination.	BacT/ALERT® bottles require storage at 15-30°C but were stored in an unmonitored room. The cryovessels used to store cryopreserved cells are in a room accessed by non-CTL staff. Vessels were not labelled as for CTL use only and were not sufficiently secure in that the power switches were exposed and not protected from accidental disruption of the power supply. The power switch for the system that monitors the temperature of the -80°C freezer was similarly unprotected. ***The establishment took action to address this shortfall before the issue of the final report. The HTA now assess this standard as fully met.***	**Minor**
PFE5 Equipment is appropriate for use, maintained, quality assured, validated and where appropriate monitored.		
a) Critical equipment and technical devices are identified, validated, regularly inspected and records are maintained.	The establishment did not provide any data to demonstrate the monitoring of the incubators used to incubate plates used in environmental monitoring. ***The establishment took action to address this shortfall before the issue of the final report. The HTA now assess this standard as fully met.***	**Minor**
e) There are documented agreements with maintenance companies.	The establishment did not provide any documented agreements for the maintenance of the incubators used to incubate plates used in environmental monitoring. ***The establishment took action to address this shortfall before the issue of the final report. The HTA now assess this standard as fully met.***	**Minor**

Advice

The HTA advises the DI to consider the following to further improve practices:

No.	Standard	Advice
1.	C2b	The DI is advised to ensure that the consent process for participation in clinical trials includes the consent for biological tests that will be carried out on blood samples.
2.	GQ1a	The DI is advised to review the SOP covering release criteria to ensure that the acceptance criteria for haematocrit levels and viability are incorporated.
3.	GQ2d	The establishment currently carries out CFU-GM assays routinely for every fifth unit that requires cryopreservation. The DI is advised to consider a review of this arrangement to ensure that the system evaluates units that represent an appropriate selection of units e.g. small volumes, multiple bags, and different cell types.
4.	GQ3f	The DI is advised to include training on all relevant legislation as part of the GOSH induction for staff involved in licensable activities.
5.	GQ4b	The DI is advised to introduce a check step that acknowledges that an accurate copy has been made when laminated processing worksheets used in the clean laboratory are copied for retention in the processing records.
6.	GQ4h	The DI is advised to ensure that all data required for traceability purposes in the virology laboratory is kept for 10 years.
7.	GQ5a	The establishment does not routinely test allogeneic donors for hepatitis e virus (HEV) by NAT. The DI is advised to follow the recommendations of the Committee for the Safety of Blood Tissues and Organs (SaBTO) regarding HEV testing.
8.	GQ6d	The SEC-DI should be applied to records that accompany tissues and cells procured for the purpose of ATMP processing.
9.	PFE2b	The establishment's procedures state that the weekly EM procedure should also be carried out when the room is manned once a month. The DI is advised to put a mechanism in place to ensure that this operational monitoring takes place as expected.
10.	PFE3a	The DI is advised to consider moving the research samples stored within the -80°C used for the passive freezing of stem cells. This would reduce the risk of the freezer being opened in error during cryopreservation.
11.	PFE5b	The DI should ensure that maintenance reports by engineers who maintain the whole site are reviewed by staff responsible for the critical equipment used in activities carried out under this licence.

Concluding comments

The HTA saw several examples of good practice during the course of the inspection, including a reciprocal QA arrangement with other laboratories in relation to the T cell depletion work undertaken by processing staff to ensure enumeration is measured

consistently. There is a good relationship with the establishment responsible for apheresis with representatives attending GOSH quality meetings. A series of ‘endpoints’ are being added to SOPs when they are updated; these summarise and highlight the key points of action in the SOP. The thymus team maintain good contacts with the US team that are the only other team worldwide responsible for this processing currently. The laboratory has begun a stability programme looking at the potency of thawed samples that have been cryopreserved for one, two, three, four and five years.

There are a number of areas of practice that require improvement, including two major shortfalls and eight minor shortfalls. These included governance and quality and premises, facilities and equipment.

The HTA requires that the Designated Individual addresses the shortfalls by submitting a completed corrective and preventative action (CAPA) plan within 14 days of receipt of the final report (refer to Appendix 2 for recommended timeframes within which to complete actions). The HTA will then inform the establishment of the evidence required to demonstrate that the actions agreed in the plan have been completed.

The HTA has assessed the establishment as suitable to be licensed for the activities specified subject to corrective and preventative actions being implemented to meet the shortfalls identified during the inspection.

Report sent to DI for factual accuracy: 20 June 2018

Report returned from DI: No factual accuracy or request for redaction comments were made by the DI

Final report issued: 13 July 2018

Completion of corrective and preventative actions (CAPA) plan

Based on information provided, the HTA is satisfied that the establishment has completed the agreed actions in the CAPA plan and in doing so has taken sufficient action to correct all shortfalls addressed in the Inspection Report.

Date: 25 September 2018

Appendix 1: HTA standards

The HTA standards applicable to this establishment are shown below; those not assessed during the inspection are shown in grey text. Individual standards which are not applicable to this establishment have been excluded.

Human Tissue (Quality and Safety for Human Application) Regulations 2007 Standards

Consent

Standard
C1 Consent is obtained in accordance with the requirements of the HT Act 2004, the Human Tissue (Quality and Safety for Human Application) Regulations 2007 and as set out in the HTA's Codes of Practice.
a) If the establishment acts as a procurer of tissues and / or cells, there is an established process for acquiring donor consent which meets the requirements of the HT Act 2004 the Human Tissue (Quality and Safety for Human Application) Regulations 2007 (Q&S Regulations) and the HTA's Codes of Practice
b) If there is a third party procuring tissues and / or cells on behalf of the establishment the third party agreement ensures that consent is obtained in accordance with the requirements of the HT Act 2004, the Q&S Regulations and the HTA's Codes of Practice.
c) The establishment or the third party's procedure on obtaining donor consent includes how potential donors are identified and who is able to take consent.
d) Consent forms comply with the HTA Codes of Practice.
e) Completed consent forms are included in records and are made accessible to those using or releasing tissue and / or cells for a Scheduled Purpose.
C2 Information about the consent process is provided and in a variety of formats.
a) The procedure on obtaining consent details what information will be provided to donors. As a minimum, the information specified by Directions 002/2018 is included.
b) If third parties act as procurers of tissues and / or cells, the third party agreement details what information will be provided to donors. As a minimum, the information specified by Directions Directions 002/2018 is included.
c) Information is available in suitable formats and there is access to independent interpreters when required.
d) There are procedures to ensure that information is provided to the donor or donor's family by trained personnel.
C3 Staff involved in seeking consent receive training and support in the implications and essential requirements of taking consent.
a) Staff involved in obtaining consent are provided with training on how to take informed consent in accordance with the requirements of the HT Act 2004 and Code of Practice on Consent.
b) Training records are kept demonstrating attendance at training on consent.

Governance and Quality

Standard
GQ1 All aspects of the establishment's work are supported by ratified documented policies and procedures as part of the overall governance process.
a) There is an organisational chart clearly defining the lines of accountability and reporting relationships.
b) There are procedures for all licensable activities that ensure integrity of tissue and / or cells and minimise the risk of contamination.
c) There are regular governance meetings, for example health and safety, risk management and clinical governance committees, which are recorded by agendas and minutes.
d) There is a document control system to ensure that changes to documents are reviewed, approved, dated and documented by an authorised person and only current documents are in use.
e) There are procedures for tissue and / or cell procurement, which ensure the safety of living donors.
g) There are procedures to ensure that an authorised person verifies that tissues and / or cells received by the establishment meet required specifications.
h) There are procedures for the management and quarantine of non-conforming consignments or those with incomplete test results, to ensure no risk of cross contamination.
i) There are procedures to ensure tissues and / or cells are not released from quarantine until verification has been completed and recorded.
j) There are procedures detailing the critical materials and reagents used and where applicable, materials and reagents meet the standards laid down by the European directives on medical devices and in vitro diagnostic medical devices.
k) There is a procedure for handling returned products.
l) There are procedures to ensure that in the event of termination of activities for whatever reason, stored tissues and / or cells are transferred to another licensed establishment or establishments.
m) The criteria for allocating tissues and / or cells to patients and health care institutions are documented and made available to these parties on request.
o) There is a complaints system in place.
p) There are written agreements with third parties whenever an activity takes place that has the potential to influence the quality and safety of human tissues and / or cells.
q) There is a record of agreements established with third parties.
r) Third party agreements specify the responsibilities of the third party and meet the requirements set out in Directions 002/2018.
s) Third party agreements specify that the third party will inform the establishment in the event of a serious adverse reaction or event.
t) There are procedures for the re-provision of service in an emergency.

GQ2 There is a documented system of quality management and audit.
a) There is a quality management system which ensures continuous and systematic improvement.
b) There is an internal audit system for all licensable activities.
c) An audit is conducted in an independent manner at least every two years to verify compliance with protocols and HTA standards, and any findings and corrective actions are documented.
d) Processes affecting the quality and safety of tissues and / or cells are validated and undergo regular evaluation to ensure they continue to achieve the intended results.
GQ3 Staff are appropriately qualified and trained in techniques relevant to their work and are continuously updating their skills.
a) There are clearly documented job descriptions for all staff.
b) There are orientation and induction programmes for new staff.
c) There are continuous professional development (CPD) plans for staff and attendance at training is recorded.
d) There is annual documented mandatory training (e.g. health and safety and fire).
e) Personnel are trained in all tasks relevant to their work and their competence is recorded.
f) There is a documented training programme that ensures that staff have adequate knowledge of the scientific and ethical principles relevant to their work, and the regulatory context.
g) There is a documented training programme that ensures that staff understand the organisational structure and the quality systems used within the establishment.
h) There is a system of staff appraisal.
i) Where appropriate, staff are registered with a professional or statutory body.
j) There are training and reference manuals available.
k) The establishment is sufficiently staffed to carry out its activities.
GQ4 There is a systematic and planned approach to the management of records.
a) There are procedures for the creation, identification, maintenance, access, amendment, retention and destruction of records.
b) There is a system for the regular audit of records and their content to check for completeness, legibility and accuracy and to resolve any discrepancies found.
c) Written records are legible and indelible. Records kept in other formats such as computerised records are stored on a validated system.
d) There is a system for back-up / recovery in the event of loss of computerised records.
e) The establishment keeps a register of the types and quantities of tissues and / or cells that are procured, tested, preserved, processed, stored and distributed or otherwise disposed of, and on the origin and destination of tissues and cells intended for human application.

f) There are procedures to ensure that donor documentation, as specified by Directions 002/2018, is collected and maintained.
g) There is a system to ensure records are secure and that donor confidentiality is maintained in accordance with Directions 002/2018.
h) Raw data which are critical to the safety and quality of tissues and cells are kept for 10 years after the use, expiry date or disposal of tissues and / or cells.
i) The minimum data to ensure traceability from donor to recipient as required by Directions 002/2018 are kept for 30 years after the use, expiry or disposal of tissues and / or cells.
j) Records are kept of products and material coming into contact with the tissues and / or cells.
k) There are documented agreements with end users to ensure they record and store the data required by Directions 002/2018.
l) The establishment records the acceptance or rejection of tissue and / or cells that it receives and in the case of rejection why this rejection occurred.
m) In the event of termination of activities of the establishment a contingency plan to ensure records of traceability are maintained for 10 or 30 years as required.
GQ5 There are documented procedures for donor selection and exclusion, including donor criteria.
a) Donors are selected either by the establishment or the third party acting on its behalf in accordance with the criteria required by Directions 002/2018.
b) The testing of donors by the establishment or a third party on behalf of the establishment is carried out in accordance with the requirements of Directions 002/2018.
c) In cases other than autologous donors, donor selection is carried out by authorised personnel and signed and reviewed by a qualified health professional.
d) There is a system in place either at the establishment or at a third party acting on its behalf to record results of donor selection and associated tests.
e) Testing of donor samples is carried out using CE marked diagnostic tests.
f) Samples taken for donor testing are clearly labelled with the time and place the sample was taken and a unique donor identification code.
GQ6 A coding and records system facilitates traceability of tissues and / or cells, ensuring a robust audit trail.
a) There is a donor identification system which assigns a unique code to each donation and to each of the products associated with it.
b) An audit trail is maintained, which includes details of when the tissues and / or cells were acquired and from where, the uses to which the tissues and / or cells were put, when the tissues and / or cells were transferred elsewhere and to whom.
c) The establishment has procedures to ensure that tissues and / or cells imported, procured, processed, stored, distributed and exported are traceable from donor to recipient and vice versa.
d) The requirements of the Single European Code are adhered to as set out in Directions 002/2018.

GQ7 There are systems to ensure that all adverse events, reactions and/or incidents are investigated promptly.
a) There are procedures for the identification, reporting, investigation and recording of adverse events and reactions, including documentation of any corrective or preventative actions.
b) There is a system to receive and distribute national and local information (e.g. HTA regulatory alerts) and notify the HTA and other establishments as necessary of serious adverse events or reactions.
c) The responsibilities of personnel investigating adverse events and reactions are clearly defined.
d) There are procedures to identify and decide the fate of tissues and / or cells affected by an adverse event, reaction or deviation from the required quality and safety standards.
e) In the event of a recall, there are personnel authorised within the establishment to assess the need for a recall and if appropriate initiate and coordinate a recall.
f) There is an effective, documented recall procedure which includes a description of responsibilities and actions to be taken in the event of a recall including notification of the HTA and pre-defined times in which actions must be taken.
g) Establishments distributing tissue and / or cells provide information to end users on how to report a serious adverse event or reaction and have agreements with them specifying that they will report these events or reactions.
h) Establishments distributing tissues and / or cells have systems to receive notifications of serious adverse events and reactions from end users and notify the HTA.
GQ8 Risk assessments of the establishment's practices and processes are completed regularly and are recorded and monitored appropriately.
a) There are documented risk assessments for all practices and processes.
b) Risk assessments are reviewed regularly, as a minimum annually or when any changes are made that may affect the quality and safety of tissues and cells.
c) Staff can access risk assessments and are made aware of local hazards at training.
d) A documented risk assessment is carried out to decide the fate of any tissue and / or cells stored prior to the introduction of a new donor selection criteria or a new processing step, which enhances the quality and safety of tissue and / or cells.

Premises, Facilities and Equipment

Standard
PFE1 The premises are fit for purpose.
a) A risk assessment has been carried out of the premises to ensure that they are fit for purpose.
b) There are procedures to review and maintain the safety of staff, visitors and patients.
c) The premises have sufficient space for procedures to be carried out safely and efficiently.
d) Where appropriate, there are procedures to ensure that the premises are of a standard that ensures the dignity of deceased persons.

e) There are procedures to ensure that the premises are secure and confidentiality is maintained.
f) There is access to a nominated, registered medical practitioner and / or a scientific advisor to provide advice and oversee the establishment's medical and scientific activities.
PFE2 Environmental controls are in place to avoid potential contamination.
a) Tissues and / or cells stored in quarantine are stored separately from tissue and / or cells that have been released from quarantine.
b) Where processing of tissues and / or cells involves exposure to the environment, it occurs in an appropriate, monitored environment as required by Directions 002/2018.
c) There are procedures for cleaning and decontamination.
d) Staff are provided with appropriate protective clothing and equipment that minimise the risk of contamination of tissue and / or cells and the risk of infection to themselves.
PFE3 There are appropriate facilities for the storage of tissues and / or cells, consumables and records.
a) Tissues, cells, consumables and records are stored in secure environments and precautions are taken to minimise risk of damage, theft or contamination.
b) There are systems to deal with emergencies on a 24 hour basis.
c) Tissues and / or cells are stored in controlled, monitored and recorded conditions that maintain tissue and / or cell integrity.
d) There is a documented, specified maximum storage period for tissues and / or cells.
PFE4 Systems are in place to protect the quality and integrity of tissues and / or cells during transport and delivery to its destination.
a) There is a system to ensure tissue and / or cells are not distributed until they meet the standards laid down by Directions 002/2018.
b) There are procedures for the transport of tissues and / or cells which reflect identified risks associated with transport.
c) There is a system to ensure that traceability of tissues and / or cells is maintained during transport.
d) Records are kept of transportation and delivery.
e) Tissues and / or cells are packaged and transported in a manner and under conditions that minimise the risk of contamination and ensure their safety and quality.
f) There are third party agreements with courier or transport companies to ensure that any specific transport conditions required are maintained.
g) Critical transport conditions required to maintain the properties of tissue and / or cells are defined and documented.
h) Packaging and containers used for transportation are validated to ensure they are fit for purpose.
i) Primary packaging containing tissues and / or cells is labelled with the information required by Directions.

j) Shipping packaging containing tissues and / or cells is labelled with the information required by Directions.
PFE5 Equipment is appropriate for use, maintained, quality assured, validated and where appropriate monitored.
a) Critical equipment and technical devices are identified, validated, regularly inspected and records are maintained.
b) Critical equipment is maintained and serviced in accordance with the manufacturer's instructions.
c) Equipment affecting critical processes and storage parameters is identified and monitored to detect malfunctions and defects and procedures are in place to take any corrective actions.
d) New and repaired equipment is validated before use and this is documented.
e) There are documented agreements with maintenance companies.
f) Cleaning, disinfection and sanitation of critical equipment is performed regularly and this is recorded.
g) Instruments and devices used for procurement are sterile, validated and regularly maintained.
h) Users have access to instructions for equipment and receive training in the use of equipment and maintenance where appropriate.
i) Staff are aware of how to report an equipment problem.
j) For each critical process, the materials, equipment and personnel are identified and documented.
k) There are contingency plans for equipment failure.

Disposal

Standard
D1 There is a clear and sensitive policy for disposing of tissues and / or cells.
a) The disposal policy complies with HTA's Codes of Practice.
b) The disposal procedure complies with Health and Safety recommendations.
c) There is a documented procedure on disposal which ensures that there is no cross contamination.
D2 The reasons for disposal and the methods used are carefully documented.
a) There is a procedure for tracking the disposal of tissue and / or cells that details the method and reason for disposal.
b) Disposal arrangements reflect (where applicable) the consent given for disposal.

Human Tissue Act 2004 Standards

Consent standards
C1 Consent is obtained in accordance with the requirements of the Human Tissue Act 2004 (HT Act) and as set out in the code of practice
a) Consent procedures are documented and these, along with any associated documents, comply with the HT Act and the HTA's Codes of Practice. b) Consent forms are available to those using or releasing relevant material for a scheduled purpose. c) Where applicable, there are agreements with other parties to ensure that consent is obtained in accordance with the requirements of the HT Act and the HTA's Codes of Practice. d) Written information is provided to those from whom consent is sought, which reflects the requirements of the HT Act and the HTA's Codes of Practice. e) Language translations are available when appropriate. f) Information is available in formats appropriate to the situation.
C2 Staff involved in seeking consent receive training and support in the essential requirements of taking consent
a) There is suitable training and support of staff involved in seeking consent, which addresses the requirements of the HT Act and the HTA's Codes of Practice. b) Records demonstrate up-to-date staff training. c) Competency is assessed and maintained.

Governance and quality system standards
GQ1 All aspects of the establishments work are governed by documented policies and procedures as part of the overall governance process
a) Ratified, documented and up-to-date policies and procedures are in place, covering all licensable activities. b) There is a document control system. c) There are change control mechanisms for the implementation of new operational procedures. d) Matters relating to HTA-licensed activities are discussed at regular governance meetings, involving establishment staff. e) There is a system for managing complaints.
GQ2 There is a documented system of audit
a) There is a documented schedule of audits covering licensable activities. b) Audit findings include who is responsible for follow-up actions and the timeframes for completing these.

GQ3 Staff are appropriately qualified and trained in techniques relevant to their work and are continuously updating their skills
a) Qualifications of staff and all training are recorded, records showing attendance at training.
b) There are documented induction training programmes for new staff.
c) Training provisions include those for visiting staff.
d) Staff have appraisals and personal development plans.
GQ4 There is a systematic and planned approach to the management of records
a) There are suitable systems for the creation, review, amendment, retention and destruction of records.
b) There are provisions for back-up / recovery in the event of loss of records.
c) Systems ensure data protection, confidentiality and public disclosure (whistleblowing).
GQ5 There are systems to ensure that all adverse events are investigated promptly
a) Staff are instructed in how to use incident reporting systems.
b) Effective corrective and preventive actions are taken where necessary and improvements in practice are made.
GQ6 Risk assessments of the establishment's practices and processes are completed regularly, recorded and monitored
a) There are documented risk assessments for all practices and processes requiring compliance with the HT Act and the HTA's Codes of Practice.
b) Risk assessments are reviewed regularly.
c) Staff can access risk assessments and are made aware of risks during training.

Traceability standards
T1 A coding and records system facilitates the traceability of bodies and human tissue, ensuring a robust audit trail
a) There is an identification system which assigns a unique code to each donation and to each of the products associated with it.
b) A register of donated material, and the associated products where relevant, is maintained.
c) An audit trail is maintained, which includes details of: when and where the bodies or tissue were acquired and received; the consent obtained; all sample storage locations; the uses to which any material was put; when and where the material was transferred, and to whom.
d) A system is in place to ensure that traceability of relevant material is maintained during transport.
e) Records of transportation and delivery are kept.
f) Records of any agreements with courier or transport companies are kept.
g) Records of any agreements with recipients of relevant material are kept.

T2 Bodies and human tissue are disposed of in an appropriate manner
a) Disposal is carried out in accordance with the HTA's Codes of Practice. b) The date, reason for disposal and the method used are documented.

Premises, facilities and equipment standards
PFE1 The premises are secure and fit for purpose
a) An assessment of the premises has been carried out to ensure that they are appropriate for the purpose. b) Arrangements are in place to ensure that the premises are secure and confidentiality is maintained. c) There are documented cleaning and decontamination procedures.
PFE2 There are appropriate facilities for the storage of bodies and human tissue
a) There is sufficient storage capacity. b) Where relevant, storage arrangements ensure the dignity of the deceased. c) Storage conditions are monitored, recorded and acted on when required. d) There are documented contingency plans in place in case of failure in storage area.
PFE3 Equipment is appropriate for use, maintained, validated and where appropriate monitored
a) Equipment is subject to recommended calibration, validation, maintenance, monitoring, and records are kept. b) Users have access to instructions for equipment and are aware of how to report an equipment problem. c) Staff are provided with suitable personal protective equipment.

Appendix 2: Classification of the level of shortfall (HA)

Where the HTA determines that a licensing standard is not met, the improvements required will be stated and the level of the shortfall will be classified as 'Critical', 'Major' or 'Minor'. Where the HTA is not presented with evidence that an establishment meets the requirements of an expected standard, it works on the premise that a lack of evidence indicates a shortfall.

The action an establishment will be required to make following the identification of a shortfall is based on the HTA's assessment of risk of harm and/or a breach of the HT Act or associated Directions.

1. **Critical shortfall:**

   A shortfall which poses a significant direct risk of causing harm to a recipient patient or to a living donor,

Or

A shortfall which poses a significant risk to human safety and/or dignity or is a breach of the Human Tissue Act 2004 (HT Act) or associated Directions,

Or

A number of 'major' shortfalls, none of which is critical on its own, but viewed cumulatively represent a systemic failure and therefore are considered 'critical'.

A critical shortfall may result in one or more of the following:

(1) A notice of proposal being issued to revoke the licence

(2) Some or all of the licensable activity at the establishment ceasing with immediate effect until a corrective action plan is developed, agreed by the HTA and implemented.

(3) A notice of suspension of licensable activities

(4) Additional conditions being proposed

(5) Directions being issued requiring specific action to be taken straightaway

2. Major shortfall:

A non-critical shortfall.

A shortfall in the carrying out of licensable activities which poses an indirect risk to the safety of a donor or a recipient

or

A shortfall in the establishment's quality and safety procedures which poses an indirect risk to the safety of a donor or a recipient;

or

A shortfall which indicates a major deviation from the Human Tissue (Quality and Safety for Human Application) Regulations 2007 or the HTA Directions;

or

A shortfall which indicates a breach in the relevant Codes of Practices, the HT Act and other relevant professional and statutory guidelines;

or

A shortfall which indicates a failure to carry out satisfactory procedures or a failure on the part of the designated individual to fulfil his or her legal duties;

or

A combination of several 'minor' shortfalls, none of which is major on its own, but which, viewed cumulatively, could constitute a major shortfall.

In response to a major shortfall, an establishment is expected to implement corrective and preventative actions within 1-2 months of the issue of the final inspection report. Major shortfalls pose a higher level of risk and therefore a shorter deadline is given, compared to minor shortfalls, to ensure the level of risk is reduced in an appropriate timeframe.

3. Minor shortfall:

A shortfall which cannot be classified as either critical or major and, which can be addressed by further development by the establishment.

This category of shortfall requires the development of a corrective action plan, the results of which will usually be assessed by the HTA either by desk based review or at the time of the next inspection.

In response to a minor shortfall, an establishment is expected to implement corrective and preventative actions within 3-4 months of the issue of the final inspection report.

Follow up actions

A template corrective and preventative action plan will be sent as a separate Word document with both the draft and final inspection report. You must complete this template and return it to the HTA within 14 days of the issue of the final report.

Based on the level of the shortfall, the HTA will consider the most suitable type of follow-up of the completion of the corrective and preventative action plan. This may include a combination of

- a follow-up site-visit inspection
- a request for information that shows completion of actions
- monitoring of the action plan completion
- follow up at next desk-based or site-visit inspection.

After an assessment of your proposed action plan you will be notified of the follow-up approach the HTA will take.