Site visit inspection report on compliance with HTA minimum standards

Centre for Cell, Gene and Tissue Therapeutics

HTA licensing number 11016

Licensed for the

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

19 – 21 July 2016

Summary of inspection findings

The HTA found the Designated Individual, the Licence Holder and the premises to be suitable in accordance with the requirements of the legislation. Since the previous inspection the establishment has commissioned a new clean room suite where processing of tissues and cells takes place.

Although the HTA found that the Centre for Cell, Gene and Tissue Therapeutics (the establishment) had met the majority of the HTA standards, shortfalls were found in relation to the Governance and Quality standards.

The establishment does not have suitable third party agreements with procurers of cells/tissues and a documented procedure for reporting Serious Adverse Events and Reactions to the HTA. Independent audits to verify compliance with all applicable HTA standards do not take place.

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.

'E*' = Establishment is licensed to carry out this activity but is not currently carrying it out.

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

'SLA' = Service level agreement with other HTA licensed establishment

Tissue type	Procurement	Testing	Processing	Storage	Distribution	Import	Export
PBSCs	**E***	**SLA**	**E**	**E**	**E**	**E**	**E**
Bone Marrow	**E***	**SLA**	**E**	**E**	**E**	**E**	**E**
Cells for DLIs	**E***	**SLA**	**E**	**E**	**E**	**E**	**E**
T-cells for virus-specific immune reconstitution	**TPA**	**SLA**	**E**	**E**	**E**	**E**	**E**

Non-transplant product – for vaccination - Lymphocytes immune therapy (LIT)	**TPA**	**SLA**	**E**	**E**	**E**		
Skin biopsies/ Bone Marrow aspirates	**TPA**	**E**	**MHRA - ATMP**				
Airways programme - Cadaveric donor and stem cells from recipient	**SLA**	**E**	**MHRA - ATMP**				

Background to the establishment and description of inspection activities undertaken

The Centre for Cell, Gene and Tissue Therapeutics, previously known as the Paul O'Gorman Laboratory, has been licensed by the HTA since 2007. The establishment is located within the Royal Free Hospital in London and is licensed for procurement, donor testing, processing, storage, distribution and import and export of tissues and cells for patient treatment. The establishment also has a Biorepository which is licensed for the storage of relevant material for scheduled purposes under the Human Tissue Act 2004 (HT Act).

The Designated Individual (DI) is the Director of the Centre and Professor of Cell and Tissue Therapy. The Royal Free London NHS Foundation Trust is the corporate licence holder and the corporate licence holder contact is the Medical Director of Transplantation. Staff employed by University College London, Royal Free Hospital, Cell Medica, Videregen Ltd and Cognate UK use the facility to process and store tissues and cells.

Cells and tissues are processed in a recently commissioned clean room suite consisting of three Grade D laboratories, five Grade B laboratories, a Book-in store and Released Goods areas. The Medicines and Healthcare products Regulatory Agency (MHRA) inspected these premises in September 2015 as the establishment holds MHRA licences, MS & MIA(IMP) 11149, for the manufacturing of advanced therapy medicinal products (ATMP), 'Specials', and investigational medicinal products (IMP). Processing of tissues/cells under the HTA licence takes place in the Grade D laboratories which contain biological safety cabinets. On occasion, biological safety cabinets in the Grade B laboratories may be used to process tissues and cells. As part of on-going environmental monitoring, and in response to advice from the MHRA, the establishment is looking into implementing a system for monitoring fungal contamination in the clean rooms.

The establishment has a well-developed system of viable and non-viable particle monitoring which includes active air sampling, contact and settle plates (both in-process and background monitoring) and in-process particle counting. There is emergency power back-up and each laboratory has its own independent air handling unit and can be individually decontaminated with hydrogen peroxide. Routine maintenance is undertaken by the Trust's Estates Department.

Cells and tissues are procured under service level agreements (SLAs) with other HTA-licensed establishments or under third party agreements (TPAs). The DI takes responsibility to train staff at other establishments to procure tissues and cells in accordance with documented standard operating procedures.

The establishment has an SLA with a 'Pathology Partnership' which is licensed by the HTA for donor testing. Third party agreements are in place with a courier for distribution of tissues and cells.

Microbiology testing of cells and tissues using broth cultures and identification of any organisms detected during environmental monitoring – settle plates, finger dabs and contact plates - are undertaken by the Microbiology Department at the Royal Free Hospital. Environmental records and product sterility testing results are reviewed before products are released.

All tissues and cells received for processing in the clean room suite or storage in the Biorepository are allocated a unique International Standard for Blood and Transplant (ISBT 128) barcode number. The customised CCGTT Electronic Records System (ERS) uses this number to track processing and storage of the relevant products. Staff check donor/recipient details (name, hospital number, date of birth), ISBT 128 label, prescription form or product request before incoming samples are booked into the system.

The CCGTT storage area has six liquid nitrogen tanks for storage of cells and tissues for patient treatment and three liquid nitrogen tanks for storage of Biorepository samples. The liquid nitrogen tanks are connected to an automated fill system. Storage temperatures are continuously monitored using a proprietary monitoring system with local alarms and a 24/7 system to alert members of staff in the event of equipment failure. The temperature of each storage tank can be checked remotely and monitored to enable trending and early warning of equipment failure.

The inspection was the fifth routine inspection undertaken by the HTA and included a visual inspection of the premises and meetings with the Director (DI), Head of Quality Management and Quality Assurance, GMP Facilities Manager, Head of IT and Deputy Lead for Biorepository, Manufacturing Scientist, GMP production Scientist, and Biorepository Technician.

The inspection covered areas where processing and storage of tissues and cells for patient treatment takes place as well as areas where relevant material was being stored for scheduled purposes. The clean room was not inspected in detail as the airflow, pressure cascades, gowning procedures, aseptic processing competency assessments undertaken using the six monthly universal broth tests were reviewed during the MHRA inspection undertaken in September 2015.

Licensable activities relating to human application:

1. **Procurement, testing, processing, storage and distribution of stem cells and donor lymphocytes from blood and bone marrow and processing of whole blood for lymphocyte immunotherapy**

The establishment is accredited by the Joint Accreditation Committee – International Society for Cellular Therapy and European Society for Blood and Marrow Transplantation (JACIE) and was last inspected in November 2013. Procurement of peripheral blood stem cells (PBSCs), bone marrow and therapeutic T-cells (DLI) ceased in November 2015. However, the establishment continues to process and store stem cells under an SLA with another HTA-licensed establishment.

The establishment processes whole blood for lymphocyte immunotherapy. Whole blood from

the partners of women who have undergone recurrent miscarriages due to possible alloimmune-mediated pregnancy loss is procured under a TPA. The blood is enriched for mononuclear cells which are administered to the mother within the first six weeks of pregnancy. Initial donor screening results are received within 30 days before the date of procurement. Mandatory testing is undertaken on donor plasma and serum samples obtained from blood taken on the day of procurement.

2. T-cell selection

Cell Medica Limited uses Streptamer technology to select for CMV antigen specific T-cells (Cytovir CMV) used to prevent or treat cytomegalovirus infection following allogeneic, haematopoietic stem cell transplantation. This cellular therapy product has been available in the UK since October 2015.

3. Clinical trials

The establishment is involved in several clinical trials where blood, skin or other relevant cells/tissues are procured under TPAs and sent to the CCGTT for use as starting materials to manufacture investigational medicinal products. The HTA only regulates the procurement and donor testing of the cells/tissues in these instances; the manufacturing, distribution and pharmacovigilance of the products is regulated by the MHRA.

- **Pro T4 trial -** isolation of CD4 T-cells from blood collected from the sibling donor who previously donated stem cells to treat an HLA-identical sibling recipient with haematological cancer.
- **ASPIRE trial and CITADEL trial** – isolation of Adenovirus or Epstein Barr virus specific T-cells respectively from blood from donors for expansion and infusion into recipients.
- **iPSC trial** – procurement of skin biopsies to produce induced pluripotent stem cells (iPSC) for autologous treatment of age-related macular degeneration.
- **ASCAT** (Autologous Stem Cells in Achilles Tendinopathy) – culture and expansion of stem cells from bone marrow aspirate for implantation into a diseased human tendon.
- **Airways programme -** undertaken in collaboration with NHSBT (HTA licence no: 11018). The larynx or trachea from a deceased donor is decellularised and repopulated with stem cells isolated from bone marrow aspirates from a donor with end stage laryngotracheal stenosis (RegenVox trial) or a damaged trachea (Inspire trial).

A document review was carried out encompassing: Standard Operating Procedures (SOPs), records of training and re-validation of staff gowning procedure and aseptic technique (broth test), equipment maintenance, meeting minutes, change management and risk assessments, incident management, agreements with third parties, audit schedule and audit reports.

Audit trails were carried out on five products, including an example of a processed PBSCs, DLIs, a lymphocyte immunotherapy product, selected CD4 lymphocytes (Pro T4 trial) and a Cytovir CMV cell product. Records of receipt and donor testing of cells and tissue procurement by third parties associated with the RegenVox and iPSC trials were reviewed. Consent records, records of donor testing, receipt of cells and tissues, processing, records of consumables used during processing cryopreservation and storage, environmental monitoring records and temperature records during transport as appropriate, were reviewed.

Licensable activities relating to storage of relevant material for Research:

1. Biorepository

The Biorepository was established in 2009, has five members of staff and can potentially store up to one million samples. Samples are stored in liquid nitrogen storage tanks or in -

80^0C freezers. Most samples in storage are under National Research Ethics Service (NRES) Ethics approval. However, the repository will also store material where NRES Ethics approval has ended. Agreements are in place to ensure that consent for research has been obtained and the Biorepository staff undertake regular audits of consent forms.

Each sample has a unique Biobank ISBT 128 number which is used to track the sample from receipt to processing, storage location and release. The SOPs cover all key activities from receipt, processing as required by clients, sample tracking and storage.

The establishment has applied to renew favourable ethical opinion given by the NRES for the UCL-RFH Biobank (REC reference 11/WA/0077), which lapsed in July 2016. The establishment stopped considering applications for release of tissue and intends to resume distribution once the renewal has been approved.

A document review was carried out. SOPs, equipment maintenance records, incident management, meeting minutes and audit reports were reviewed. Electronic records including the Biorepository database and temperature monitoring data were reviewed. Three audit trails from consent to storage location as recorded in the database and within paper files were carried out; there were no discrepancies.

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.		
r) Third party agreements specify the responsibilities of the third party and meet the requirements set out in Directions 003/2010.	The establishment has many third party agreements (TPAs) with procurers of tissues and cells. Not all TPAs currently in place clearly outline the responsibilities of the third party including the requirement (as appropriate) to provide a blood sample taken on the day of procurement and to inform the CCGTT of any serious adverse events and reactions (SAEARs) relating to procurement in a timely manner.	**Minor**
s) Third party agreements specify that the third party will inform the establishment in the event of a serious adverse reaction or event.		

GQ2 There is a documented system of quality management and audit.		
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.	Independent audits to verify compliance with all applicable HTA standards are not undertaken by persons who do not work under the licence. However, internal audits by staff who work under the licence do take place at regular intervals.	**Minor**
GQ7 There are systems to ensure that all adverse events are investigated promptly.		
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.	The establishment does not have a documented procedure for identifying and reporting SAEARs to the HTA. In addition, the process for receiving and acting on notifications of adverse events from end users has not been formalised. The establishment does however, identify and investigate internal incidents and implements corrective and preventative actions which are disseminated during regular quality meetings. There is the risk that in the absence of the DI, key members of staff will not be familiar with the process of identifying and reporting SAEARs to the HTA.	**Minor**
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.		
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.		

Advice

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

No.	Standard	Advice
1.	GQ1	The DI is advised to appoint Persons Designated on the licence and inform the HTA of the names and contact details of the relevant people.
2.	GQ1j	The DI is advised to detail the specification of the Streptamer multimers (MHC-antigen multimers) used to isolate CMV cells and to implement a system of checks to ensure that multimers provided by the manufacturer meet the required specifications.
3.	GQ2d	The DI is advised to consider obtaining and reviewing engraftment data relating to recipients, whenever stem cells are released to end users. This will help to

		provide assurance that cells released from the CCGTT meet the requirements for quality and safety.

Human Tissue Act 2004 Standards

No.	Standard	Advice
4.	GQ2	The DI is advised to consider strengthening the audit process undertaken by the Biorepository and record the name of the person who undertook each audit, document the follow up actions and record the name of the person who is responsible for each action.

Concluding comments

The establishment has experienced, long-serving staff who work together to develop, validate and implement novel procedures. The DI, Head of Quality Management and Quality Assurance, GMP Facilities Manager and Head of IT work well together to ensure there is effective management of staff, facilities and processes.

There are regular quality meetings where staff discuss non-conformances, audits, training needs and any changes to procedures. All staff who work in the clean room attend monthly meetings where clean room-specific matters are discussed. Staff are provided with training opportunities and take pride in the quality of service they provide. A member of staff is responsible for monthly checks on orders and expiry dates of consumables in stock.

There are a number of areas of practice identified during the inspection that require improvement, including four minor shortfalls. The HTA has given advice to the Designated Individual with respect to appointing Persons Designated on the licence, critical consumables, monitoring engraftment data and audits undertaken by the Biorepository.

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: 6 September 2016

Report returned from DI: 7 October 2016

Final report issued: 20 December 2016

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: 20 November 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 003/2010 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 003/2010 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.
f) There are procedures for tissue and / or cell procurement, which ensure the dignity of deceased 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.
n) The establishment ensures imports from non EEA states meet the standards of quality and safety set out in Directions 003/2010.
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 003/2010.
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 003/2010, is collected and maintained.
g) There is a system to ensure records are secure and that donor confidentiality is maintained in accordance with Directions 003/2010.
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 003/2010 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 003/2010.
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 003/2010.
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 003/2010.
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.
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 003/2010.
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 003/2010.

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
• Consent forms comply with the HTA's Code of Practice • Consent forms are in records and are made accessible to those using or releasing relevant material for a scheduled purpose • If the establishment obtains consent, a process is in place for acquiring consent in accordance with the requirements of the HT Act 2004 and the HTA's Codes of Practice • Where applicable, there are agreements with third parties to ensure that consent is obtained in accordance with the requirements of the HT Act 2004 and the HTA's Codes of Practice • Consent procedures have been ethically approved
C2 Information about the consent process is provided and in a variety of formats
• Standard operating procedures (SOPs) detail the procedure for providing information on consent • Agreements with third parties contain appropriate information • Independent interpreters are available when appropriate • Information is available in suitable formats, appropriate to the situation • Consent procedures have been ethically approved

C3 Staff involved in seeking consent receive training and support in the implications and essential requirements of taking consent
• Standard operating procedures (SOPs) detail the consent process • Evidence of suitable training of staff involved in seeking consent • Records demonstrate up-to-date staff training • Competency is assessed and maintained

Governance and quality system standards
GQ1 All aspects of the establishments work are supported by ratified documented policies and procedures as part of the overall governance process
• Policies and procedures are in place, covering all activities related to the storage of relevant material for research in connection with disorders, or the functioning, of the human body • Appropriate risk management systems are in place • Regular governance meetings are held; for example, health and safety and risk management committees, agendas and minutes • Complaints system
GQ2 There is a documented system of quality management and audit
• A document control system, covering all documented policies and standard operating procedures (SOPs). • Schedule of audits • Change control mechanisms for the implementation of new operational procedures
GQ3 Staff are appropriately qualified and trained in techniques relevant to their work and are continuously updating their skills
• Qualifications of staff and training are recorded, records showing attendance at training • Orientation and induction programmes • Documented training programme, (e.g. health and safety, fire, risk management, infection control), including developmental training • Training and reference manuals • Staff appraisal / review records and personal development plans are in place
GQ4 There is a systematic and planned approach to the management of records
• Documented procedures for the creation, amendment, retention and destruction of records • Regular audit of record content to check for completeness, legibility and accuracy • Back-up / recovery facility in the event of loss of records

- Systems ensure data protection, confidentiality and public disclosure (whistle-blowing)

GQ5 There are documented procedures for distribution of body parts, tissues or cells

- A process is in place to review the release of relevant material to other organisations
- An agreement is in place between the establishment and the organisation to whom relevant material is supplied regarding the tracking and use of material and eventual disposal or return

GQ6 A coding and records system facilitates traceability of bodies, body parts, tissues and cells, ensuring a robust audit trail

- There is an identification system which assigns a unique code to each donation and to each of the products associated with it
- An audit trail is maintained, which includes details of when and where the relevant material was acquired, the consent obtained, the uses to which the material was put, when the material was transferred and to whom

GQ7 There are systems to ensure that all adverse events are investigated promptly

- Corrective and preventive actions are taken where necessary and improvements in practice are made
- System to receive and distribute national and local information (e.g. HTA communications)

GQ8 Risk assessments of the establishment's practices and processes are completed regularly and are recorded and monitored appropriately

- Documented risk assessments for all practices and processes
- Risk assessments are reviewed when appropriate
- Staff can access risk assessments and are made aware of local hazards at training

Premises, facilities and equipment standards

PFE1 The premises are fit for purpose

- A risk assessment has been carried out of the premises to ensure that they are appropriate for the purpose
- Policies in place to review and maintain the safety of staff, authorised visitors and students
- The premises have sufficient space for procedures to be carried out safely and efficiently
- Policies are in place to ensure that the premises are secure and confidentiality is maintained

PFE 2 Environmental controls are in place to avoid potential contamination
• Documented cleaning and decontamination procedures • Staff are provided with appropriate protective equipment and facilities that minimise risks from contamination • Appropriate health and safety controls are in place
PFE3 There are appropriate facilities for the storage of bodies, body parts, tissues and cells, consumables and records.
• Relevant material, consumables and records are stored in suitable secure environments and precautions are taken to minimise risk of damage, theft or contamination • Contingency plans are in place in case of failure in storage area • Critical storage conditions are monitored and recorded • System to deal with emergencies on 24 hour basis • Records indicating where the material is stored in the premises
PFE 4 Systems are in place to protect the quality and integrity of bodies, body parts, tissues and cells during transport and delivery to a destination
• Documented policies and procedures for the appropriate transport of relevant material, including a risk assessment of transportation • A system is in place to ensure that traceability of relevant material is maintained during transport • Records of transportation and delivery • Records are kept of any agreements with recipients of relevant material • Records are kept of any agreements with courier or transport companies
PFE5 Equipment is appropriate for use, maintained, quality assured, validated and where appropriate monitored
• Records of calibration, validation and maintenance, including any agreements with maintenance companies • Users have access to instructions for equipment and receive training in use and maintenance where appropriate • Staff aware of how to report an equipment problem • Contingency plan for equipment failure

Disposal Standards
D1 There is a clear and sensitive policy for disposing of human organs and tissue
• Documented disposal policy • Policy is made available to the public • Compliance with health and safety recommendations
D2 The reason for disposal and the methods used are carefully documented
• Standard operating procedures (SOPs) for tracking the disposal of relevant material detail the method and reason for disposal • Where applicable, disposal arrangements reflect specified wishes

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.