Site visit inspection report on compliance with HTA minimum standards

Royal Free Hospital

HTA licensing number 11016

Licensed for the

- **procurement, processing, testing, storage, distribution and export 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**

22-24 November 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 Royal Free Hospital (the establishment) had met the majority of the HTA standards, shortfalls were found in relation to agreements with other organsiations, temperature monitoring of storage areas, adverse event reporting, environmental monitoring, and process validation under the Human Tissue (Quality and Safety for Human Application) Regulations 2007 (as amended). Shortfalls were also identified under the Human Tissue Act 2004 in relation to audits and risk assessments. The HTA also gave advice regarding the Single European Code, environmental monitoring, tissue and cells authorisation and data manipulation.

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.

Tissue Category; Tissue Type	Procurement	Processing	Testing	Storage	Distribution	Import	Export
Progenitor Cell, Hematopoietic, Bone Marrow; Bone Marrow	**E**	**E***	**E**	**E***	**E***		**E***
Progenitor Cell, Hematopoietic, PBSC; PBSC		**E**		**E**	**E**		**E***
Progenitor Cell, Hematopoietic, Unspecified; Peripheral Blood Mononuclear Cells (PBMC)	**E**	**E***		**E***	**E***		**E***

Mature Cell, T Cell (DLI); DLI	**E***	**E***		**E***	**E***		**E***
Other; Trachea (ATMP)			**E***				
Other; Skin Biopsy (ATMP)	**E***		**E***				
Reproductive, Ovarian; Ovarian Tissue	**E***	**E***	**E***	**E***	**E***		

Background to the establishment and description of inspection activities undertaken

The establishment is licensed for the procurement, processing, testing, storage, distribution and export of human tissues and cells for human application under the Human Tissue (Quality and Safety for Human Application) Regulations 2007 (as amended) (the Regulations).

Additionally, the establishment is also licensed under the Human Tissue Act 2004 (HT Act) for the storage of relevant material that has come from a human body for use for a scheduled purpose.

The establishment has been licensed by the HTA since July 2006 and this is the sixth routine site visit inspection to assess whether or not the establishment continues to meet the HTA's standards. Annual activity data, pre-inspection discussions with the DI and the establishment's Quality Manager, and the previous inspection report were used to inform the timetable that was developed for this inspection.

The establishment processes tissues and cells under the establishment's HTA Human Application licence prior to them being used for patient treatment. The establishment is also licensed by the Medicines and Healthcare Products Agency (MHRA) as a manufacturer of advance therapy medicinal products (ATMPs) and the production of specials. Donors of ATMP starting materials are tested for the mandatory infectious disease markers and have tissues and cells procured by the establishment under its HTA licence. Tissues and cells are then transferred to the authority of the establishment's MHRA licence for manufacture into ATMPs.

Under the establishment's HTA Human Application licence, the establishment undertakes various licensable activities both at its own premises and at other premises under the authority of third party agreements. In addition, the establishment has service level agreements with other licensed establishments who send tissues and cells to the establishment. These activities are summarised below.

1) The establishment receives peripheral blood stem cells (PBSCs) from adult donors for autologous use. Donors have mandatory serological infectious disease testing undertaken and have PBSCs procured via apheresis by another licensed establishment. Cells received by the establishment are cryopreserved within a grade A environment within a grade D background prior to being stored within the establishment's vapour phase liquid nitrogen storage facility. Upon request from the donor's treating hospital, cryopreserved cells are distributed back to them for end use re-infusion.
2) As part of a clinical trial, peripheral blood mononuclear cells are procured from adult donors at another HTA-licensed organisation and then sent to the establishment. Cells received by the establishment are processed within a grade A environment within a grade D background environment where they undergo a cell selection. The cells are then cryopreserved and stored within the establishment's vapour phase

liquid nitrogen storage facility. Upon request from the donor's treating hospital, cryopreserved cells are distributed back to them for end use re-infusion.

3) The establishment receives haematopoietic progenitor cells from bone marrow (HPC-M) aspirates from adult donors for autologous use. Kits for the collection of the bone marrow are prepared by the establishment and sent to another hospital who undertake the procurement under a third party agreement with the establishment. Donor serological infectious disease testing is also undertaken under the establishment's licence under the authority of the TPA. Procured bone marrow is sent to the Royal Free Hospital where it is manufactured into an ATMP under the MHRA licence.
4) The establishment is also starting a new clinical trial with similar licensable activity to that described above (item 3) where donor testing and procurement of bone marrow will take place under the establishment's HTA licence and the cells used to manufacture an ATMP under the establishment's MHRA licence.
5) Although the establishment had not yet commenced activity with ovarian tissue at the time of the inspection, a preparation process dossier has been submitted to the HTA and approved. The establishment will, in the future, be procuring, processing, cryopreserving and storing ovarian tissue for autologous end use. This proposed activity was not reviewed in detail since, to date, no activity has taken place.
6) The establishment plans to commence another new clinical trial during which donor testing will take place under a third party agreement and procurement of tumour tissue will take place under the establishment's HTA licence. The procured tissues and cells will be used to manufacture an ATMP under the establishment's MHRA licence. Again, this activity has not yet commenced; however, early draft versions of associated standard operating procedures were reviewed for information purposes during the inspection.

Audits were carried out during the inspection.

1) Two sets of records relating to autologous PBSCs processed and stored by the establishment were reviewed. Details of cell receipt, processing, cryopreservation and post-processing sterility data were reviewed and found to be satisfactory. One minor anomaly was identified where the results from environmental monitoring settle plates had been mistakenly recorded against a data field usually used to record results relating to operator sleeve contact plates.
2) Two sets of records relating to procured cells which are subject to cell selection prior to processing, cryopreservation and storage were reviewed. Records relating to the donor, cell receipt, processing, cryopreservation and post-processing sterility data were reviewed and found to be satisfactory. One minor anomaly was identified where a cleaning checklist, that is completed by establishment staff following processing sessions, had not been filed in the processing records as expected.
3) Two sets of records relating to procured haematopoietic progenitor cells in bone marrow which are processed into an ATMP under an MHRA licence were reviewed. Donor details, records relating to the bone marrow collection kits, and receipt records were reviewed and found to be satisfactory. No anomalies were identified.

Under the establishment's HT Act licence, the establishment receives and stores relevant material from various studies taking place both internally and externally. Samples are received at the establishment which may require some form of processing, for example,

whole blood being processed into serum, plasma or buffy coat before being aliquoted into a number of small sample containers. Other samples received at the establishment do not require processing and are stored in their original collection tubes. The establishment has a range of storage facilities which include three vapour phase liquid nitrogen storage tanks, two -80°C chest freezers, one -80°C upright freezer and two -20°C freezers.

During the inspection, the inspection team observed the procedure through which newly received and processed samples are recorded onto the establishment's electronic database. The observation also included how the sample's location within the establishment's storage facility is tracked. While observing the new samples being placed into storage, details of two samples in adjacent positions within the storage facility were taken and used to audit the establishment's traceability systems. The physical locations of the samples were cross-checked against the positions recorded in the establishment's electronic database. No anomalies were identified during the audit.

The inspection team also conducted roundtable discussions with the research tissue bank staff during which procedures relating to preparing and conducting sample receipt and storage for new studies were discussed. Aspects of the research tissue bank's governance and quality systems including audit, risk assessments and staff induction and training were also discussed and reviewed.

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 002/2018.	The establishment has a third party agreement (TPA) with another organisation which tests donors and procures bone marrow under the authority of the establishment's licence. Procured samples are transferred to the Royal Free Hospital and are used as a starting material for an advanced therapy medicinal product. The TPA states that donor serological testing is performed in a 'suitably licensed laboratory'. This is not sufficient to indicate which HTA licence and therefore, which DI is responsible for the oversight of the laboratory undertaking donor testing. *Following the inspection, the establishment provided evidence to the HTA demonstrating that measures have been put in place to meet the standard prior to the release of the final report. The HTA now considers this standard to be fully met.*	**Minor** ***Fully met***
s) Third party agreements specify that the third party will inform the establishment in the event of a serious adverse reaction or event.	The establishment's TPA with the transport provider moving cells from and to other organisations does not include the requirement for the provider to alert the establishment to any adverse events that may occur so that the incidents can be reported to the HTA within 24 hours of their discovery.	**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.	The establishment uses a controlled-rate freezer (CRF) during the cryopreservation of PBSCs. In the event of a failure of the CRF or when cryopreserving PBSCs from a donor with a known infectious disease, cells are frozen using a passive freezing process within the -80^{o}C freezer and liquid nitrogen dewar. The establishment has no documented validation data with regards to the passive freezing process. Without formal validation, the establishment cannot demonstrate that the passive freezing temperature profile is as expected and is suitable to maintain the quality and safety of the PBSCs during freezing.	**Minor**
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.	In the past, during procurement of bone marrow which is used as a starting material for ATMP production, samples for donor serological testing were being taken prior to procurement. The establishment has now corrected the sampling time point so that samples for serological testing are taken at the time of procurement of the bone marrow which is in accordance with Directions 002/2018. However, the establishment has not undertaken a review of any risks to the processed cells or other cells processed in the same facility which may have arisen as a result of this case where the testing samples has been taken at the incorrect time point.	**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's serious adverse events and adverse reactions (SAEARs) procedure states that incidents should be reported to the HTA 'within 24 hours (or as soon as practically possible)'. This does not reflect the HTA's requirement that all SAEARs must be reported to the HTA within 24 hours of discovery of the event.	**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.	The establishment does not have a risk assessment in relation to the PBSCs that are processed, stored and distributed under its licence	**Minor**
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.	The establishment assesses risks as part of its change control process either when a new activity is commenced or where an existing activity changes. These risk assessments however are not reviewed annually.	**Minor**

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.	Heparinised saline is prepared within one of the establishment's microbiological safety cabinets which maintains a Grade A environment within a grade B air quality background. The establishment does not undertake monitoring of the grade B background environment during preparation of the solution.	**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.	The establishment stores reagents and consumables that have been cleared for use in the cleanrooms within a dedicated storage area. The temperature of the storage room is set at 20°C with the alarm triggering if the temperature exceeds the range of 18°C and 24°C. The cryoprotectant used during the processing of cells, should be stored at a temperature of between 20°C to 30˚C. The current temperature set point of 20ºC and the values at which the alarm is triggered are not appropriate to assure the DI that the DMSO is being stored within the temperature range specified by the manufacturer. In addition, where documentation such as for example, a certificate of analysis, is pending from a reagent or consumable supplier, reagents and consumables are quarantined in a dedicated quarantine room. This room however is not temperature monitored meaning that the DI cannot assure himself that consumables and reagents have been stored at the appropriate temperature while in quarantine.	**Minor**

Human Tissue Act 2004 Standards

Governance and Quality

Standard	Inspection findings	Level of shortfall
GQ2 There is a documented system of audit		
a) There is a documented schedule of audits covering licensable activities.	The last audit that took place within the research tissue bank was in 2017. There is no schedule of audits in place or any audits of stored tissue or consent documentation taking place at the research tissue bank.	**Minor**
b) Audit findings include who is responsible for follow-up actions and the timeframes for completing these.		
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.	There are no documented study-specific, procedure-specific or premises-specific risk assessments in place at the research tissue bank. As no risk assessments are in place standards GQ6(b) and GQ6(c) cannot be met.	**Minor**

Advice

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

No.	Standard	Advice
1.	GQ6(d)	The establishment applies the Single European Code (SEC) to PBSCs prior to their freezing. However, it is now realised that this code was incorrectly created. The establishment has proposed a suitable procedure through which the correct SEC will be added to a third bag which will be used to wrap the double-bagged frozen cells upon their release for end use. The DI is advised to develop a guidance for end users, clearly stating why there are additional, corrected SECs within the outer transport bag and to instruct the end user which SEC should be recorded in the recipients notes.
2.	GQ6(d)	Where the establishment receives cells from another HTA-licensed organisation, the delivered cells have had a full SEC applied to the cell collection bag that relates to the donor hospital. The DI is advised to liaise with the DI at the other HTA licensed organisation to request that only the SEC-DI is added to the procured cells which are then circulated to the Royal Free Hospital for processing, cryopreservation and storage.

3.	GQ8(b)	In addressing the shortfall identified against standard GQ8(b), the DI may wish to consider maintaining a copy of the risk assessments undertaken as part of the establishment's change control procedure in a separate, dedicated file. These versions of risk assessments may then be reviewed on an annual basis without the need to review all of the establishment's change control files.
4.	PFE2(b)	The DI is advised to consider implementing a procedure to monitor for contamination within the establishment's processing facility of:- • hard to reach areas such as the corners of the transfer hatches which cannot be reached using contact plates; and • areas with frequent use by multiple operators such as keyboards, hatch latches and switches.
5.	PFE4(a)	During an audit of records relating to the processing of PBSCs, some examples where records had not been maintained as expected were identified. In one case, environmental monitoring data from settle plates had been recorded incorrectly against the sleeve contact plate results. In addition, a further case where the cleaning log that is completed following each processing event had not been filed with the processing records as expected. The DI is advised to develop a checklist of all expected documentation and data that can be used to assure the establishment that all data is present and consistently recorded when reviewing processing and environmental monitoring data prior to authorising the cells as being suitable for release.
6.	GQ1(a) HT Act	The establishment develops sample processing protocols relating to the various studies which send relevant material to the establishment for storage. The DI is advised to consider sharing these sample processing protocols with the study team when the service level agreement is sent out for review. This way the study team can confirm that they accept the proposed processing protocol. This confirmation can then be stored with the signed SLA as a record of this acceptance.
7.	GQ1(d) HT Act	The lead for the research tissue bank attends the establishment's quality management and user group meetings, in addition to holding daily discussions with biobank staff. This provides a forum for governance and HT Act matters relating to the tissue bank's activity to be raised. In addition to these meetings the DI may wish to consider holding dedicated governance meetings that are specific to the research tissue bank and which could include all staff working within the tissue bank.
8.	T1(c) HT Act	Researchers requesting samples from the research repository are sent an inventory of their entire sample cohort in a spreadsheet. Researchers then sort and collate a new spreadsheet from this data so that only samples that are being requested remain in the spreadsheet. This amended 'sample request' spreadsheet is returned to the establishment where it is used as a 'picking list' to select the samples from the storage facility and to prepare them for shipping. There is considerable sorting, cutting and pasting of the spreadsheets during these operations with the review and removal of samples being a manual task. The DI is advised to develop a system through which checks can be made on the manipulated data to help assure himself that no inadvertent

		data corruption has occurred during the manipulation of the spreadsheet by either the establishment staff or researchers requesting the samples.

Concluding comments

There are a number of areas of practice that require improvement, including eleven minor shortfalls. The HTA has given advice to the Designated Individual with respect to agreements with other organisations, temperature monitoring of storage areas, adverse event reporting environmental monitoring, and process validation under the Human Tissue (Quality and Safety for Human Application) Regulations 2007 (as amended). Shortfalls were also identified under the Human Tissue Act 2004 in relation to audits and risk assessments. The HTA also gave advice regarding the single European code, environmental monitoring, tissue and cells authorisation and data manipulation.

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 December 2018

Report returned from DI: 9 January 2019

Final report issued: 29 January 2019

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: 22 November 2019

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.
n) The establishment ensures imports from non EEA states meet the standards of quality and safety set out in Directions 002/2018.
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.