Site visit inspection report on compliance with HTA minimum standards

Addenbrooke's Hospital

HTA licensing number 11066

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)**

25-26 June 2019

Summary of inspection findings

The HTA found the Designated Individual (DI), the Licence Holder (LH) and the premises to be suitable in accordance with the requirements of the legislation.

Although the HTA found that Addenbrooke's Hospital (the establishment) had met many of the HTA's standards, five minor shortfalls were found in relation to: the absence of a full independent audit; incomplete donor medical assessments; inappropriate timing of blood sampling for serology testing of certain donors; a lack of governance covering the testing of liver vessels relating to the organisation's other Human Application licence; and a lack of availability of risk assessments for staff.

Advice has been given relating to the Consent and Governance and Quality standards.

Particular examples of 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 (DI), Licence Holder (LH), premises and practices are suitable.

The statutory duties of the DI 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 licenses 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
Cardiovascular, Vessels; Vessels (including Iliac)			TPA				
Mature Cell, T Cell (DLI); DLI	E	E	TPA	E	TPA		E*
Other; Tumour (ATMP)	E		TPA				
Progenitor Cell, Hematopoietic, Bone Marrow;	E	E	TPA	E	E*		E*

Bone Marrow							
Progenitor Cell, Hematopoietic, Cord Blood; Cord Blood			**E***	**E***	**E***		**E***
Progenitor Cell, Hematopoietic, PBSC; PBSC	**E**	**E**	**TPA**	**E**	**TPA**		**E***

Background to the establishment and description of inspection activities undertaken

This report refers to the activities carried out by Addenbrooke's Hospital (the establishment), which was issued an HTA licence in August 2006. This was the sixth HTA site visit inspection of the establishment (the last inspection was in April 2017) and the first since the amended Human Tissue (Quality and Safety for Human Application) Regulations 2007 came into force on 1 April 2018 [Q&S Regulations (as amended)]. This was a routine inspection to assess whether the establishment is continuing to meet the HTA's standards.

Addenbrooke's Hospital is part of Cambridge University Hospitals NHS Foundation Trust (CUH FT). CUH FT is situated on the Cambridge Biomedical Campus, which also sites the Royal Papworth Hospital NHS FT.

The establishment is licensed under the Q&S Regulations (as amended) for the procurement, processing, testing, storage, distribution and export of tissues and cells for human application. CUH FT also has a separate licence under the Q&S Regulations (as amended) to support the non-haematopoietic transplant programme (see below).

Licensed activities take place in the Department of Haematology and Blood and Marrow Transplant (BMT), and the Department of Oncology, both within CUH FT Cancer Directorate, and in the Cambridge Cellular Therapy Laboratory (CCTL), part of the Pathology Directorate. Licensed activities also take place under the terms of a third party agreement (TPA) in the Public Health England (PHE) laboratories based in the CUH FT Pathology Directorate. A TPA is also being set up for licensed activities to take place in the Royal Papworth Hospital NHS FT (see below).

The DI is a Consultant Haematologist – Clinical Lead for Immune Effector Cell Therapy, the Corporate Licence Holder (CLH) is CUH FT and the CLH Contact (CLHC) is the CUH FT Director for Clinical Quality. There are four Persons Designated (PDs) working under the licence: the Clinical Nurse Specialist - Apheresis Unit Director; a Consultant Haematologist; the Chief Biomedical Scientist - Quality and Regulatory Affairs; and the CUH FT Compliance Manager.

The Department of Haematology and BMT currently undertakes the collection of peripheral blood stem cells (PBSC) and donor lymphocytes (for donor lymphocyte infusion, DLI). Collections are for both adult and paediatric (under the age of 18 years) autologous transplantation or are from directed, related adult donors for allogeneic transplantation at the establishment. The establishment also undertakes the collection of bone marrow (BM) from adult donors for autologous and allogeneic transplantation and from paediatric donors for autologous transplantation.

The Department of Haematology and BMT also undertakes the collection, processing and storage of PBSC for autologous transplantation for patients referred from a separate NHS FT under the terms of a service level agreement (SLA).

Tissue-typed ('matched') unrelated BM, PBSC, donor lymphocyte and umbilical cord blood donations for transplantation at the establishment are managed by the 'Anthony Nolan and

NHS Stem Cell Registry' under the terms of a service level agreement (SLA) and such collections take place at other centres.

The Department of Haematology and BMT is accredited by the Joint Accreditation Committee - International Society for Cellular Therapy (ISCT-Europe) and European Society for Blood and Marrow Transplantation (EBMT) (JACIE) and was last assessed by this organisation in January 2018. It has been JACIE-accredited since November 2007.

Procurement

Donor selection and the seeking of consent for PBSC, BM and donor lymphocyte procurement, as well as for mandatory serology tests, take place in the Haematology and BMT Day Unit and in the Paediatric Unit. Patients are consented at both the initial consultation and on the day of collection by trained staff working to specific procedures (see *Advice*, item 1). Those patients who are not suitable for autologous transplantation may receive directed, related BM or PBSC donations. In these cases, donor selection is conducted by an independent qualified medical practitioner in the Haematology and BMT Department using CUH FT donor selection forms [see shortfall against standard GQ5(a)]. Published information from haematological charities is provided about the donation process. CUH FT Cancer Directorate consent forms are used which record consent for cell mobilisation (where applicable), collection, processing, testing, storage, research and disposal.

Human leukocyte antigen tissue typing is carried out in the Department of Histocompatibility and Immunogenetics (Tissue Typing) within CUH FT.

Blood samples for serology testing are currently taken from all donors up to 30 days prior to cell collection and are sent to the PHE laboratories [see shortfall against standard GQ5(b)]. They are taken by phlebotomists and sent to the PHE laboratories by means of a pneumatic tube system (see *Advice*, item 5).

The apheresis unit within the Department, contains four apheresis machines for PBSC and donor lymphocyte collection. Following collection, cells are packaged and taken to the CCTL by establishment staff using well-defined, validated procedures.

Consumables for PBSC, donor lymphocyte and BM procurement are kept in two secure, temperature-monitored, storage areas in the apheresis unit.

BM procurement takes place in a dedicated operating theatre within the operating theatre complex. Following collection, cells are taken to the CCTL using similar procedures.

The Department of Oncology at CUH FT is involved in a clinical trial using autologous melanoma tumour tissue to derive tumour infiltrating lymphocytes (TILs) to treat advanced stage melanoma. To date, two patients have taken part in the UK arm of the trial. The tumour biopsies are used as starting material for a cell-based Advanced Therapy Investigational Medicinal Product (ATIMP). Donor selection and the seeking of consent for tissue procurement, as well as for mandatory serology tests, take place in the Department of Oncology. The donor information sheet and consent form have been approved by an ethics committee. Blood samples for serology testing are taken up to 30 days prior to cell collection and are sent to the PHE laboratories [see shortfall against standard GQ5(b)]. Tissue is shipped and processed by a Dutch company under agreement. The company provides a biopsy kit and accompanying labels on the day of the procedure. Each donation is allocated a Single European Code Donation Identification Sequence (SEC-DI). The manufactured product is returned for transplantation 6-9 weeks later.

The Department of Oncology at Papworth Hospital will be involved in a similar clinical trial using autologous lung tumour tissue to derive TILs to manufacture an ATIMP to treat advanced stage lung cancer. This will be carried out under the terms of a TPA which is currently being developed. The DI has risk assessed the relevant third party premises (RTPP) and procedures for the procurement and transport have been developed.

Processing

The CCTL processing facility consists of a clean room containing three aseptic laboratories. Each laboratory contains a laminar air flow cabinet capable of maintaining a grade A processing environment in a background of grade B. Temperature-sensitive reagents and consumables used during processing are stored in monitored and alarmed refrigerators.

Environmental monitoring is performed at rest and during processing activities and particle counts are reviewed after each procedure.

The facility is cleaned daily, with additional deep cleaning procedures performed on a monthly and quarterly basis. Cleaning agents are rotated regularly to ensure effective decontamination.

The facility performs total nucleated cell count and CD34 immunophenotype of pre-apheresis samples, and CD34/CD45 immunophenotype and cell viability assays of post-processed samples. Sterility analysis (for both bacteria and fungi) on post-processed samples is performed in the PHE laboratories.

Haematocrit levels, blood group and chimerism analyses are performed in the CUH FT core biochemical assay laboratory (CBAL).

Processing produces both cryobags and ampoules (‘pilot samples’) for each collected unit. Pilot samples allow for quality control analysis during the processing, storage and thawing steps. The establishment has acceptance criteria based on the above set of markers. Products with minimal cell counts are disposed.

Donations to be shipped offsite are allocated the full SEC. Donations to be used within CUH FT are labelled with a unique identification numbers but not the SEC.

Cryopreservation and Storage

Cryopreservation of products and pilot samples takes place using one of three validated and serviced controlled-rate freezers (CRFs) with dimethyl sulphoxide/plasma as the cryoprotectant, using an established freezing profile. Following cryopreservation, products and pilot samples are stored in the liquid nitrogen storage area in the vapour phase of two ’quarantine’ liquid nitrogen storage vessels (cryovessels) pending receipt of serology results. Once serology results, environmental monitoring data, and processing records have been reviewed by the Stem Cell Laboratory Manager, products are designated and approved for release. They are then transferred to one of 20 ‘cleared’ cryovessels. The quarantine cryovessels are also used to store serologically positive samples.

All storage containers, including cryovessels, freezers and refrigerators, are linked to a continuous temperature-monitoring unit that feeds into a wired callout system which notifies a ‘manned’ area of the building. Staff in the area are responsible for contacting the ‘on-call’ scientist. Temperature excursions outside the set ranges trigger both audible alarms and activate the callout system and the system is tested regularly. There are fixed oxygen depletion monitors linked to an alarm system in the liquid nitrogen storage area and staff carry portable monitors.

The cryovessels are linked to an automated filling system and are subject to an annual calibration under contract. One back-up cryovessel is available for contingency storage.

PBSC collections from the separate HTA-licensed NHS FT are transported to the establishment for processing using well-defined, validated procedures.

Biological function of BM (but not PBSC) products after processing and storage is assessed using colony forming unit (CFU) assays.

Distribution

Products for transplantation locally are taken to the CUH FT clinical facilities in validated dry shippers. Those to be distributed to two separate end user NHS FTs for transplantation are transported by courier working under the terms of a TPA.

Testing

The Public Health England Public Health Laboratory (PHE-PHL) network of laboratories is accredited by the United Kingdom Accreditation Service (UKAS) to International Organization for Standardization (ISO) standard 15189: 2012. The last UKAS inspection was in November 2018. Samples are tested using CE-marked diagnostic kits on automated testing equipment according to manufacturers' instructions. Antibody tests for a range of viruses and bacteria are carried out, including HTLV-1, HIV-1 and 2, HBsAg, HBc, HCV and *T. pallidum*, as well as confirmatory serology and Nucleic Acid Amplification Technique (NAT) testing.

The PHE laboratory routinely takes part in external quality assessment schemes for the above tests.

The separate CUH FT licence under the Q&S Regulations (as amended) to support the non-haematopoietic transplant programme ((HTA licensing number 11072) does not include testing. Instead, donors to that programme are tested under the current establishment's licence. This is carried out under a 'collaborative agreement' between the two DIs and is overseen by a PD working under both licences (CUH FT Compliance Manager). However, the agreement is out of date. In addition, the establishment was not aware of how many donors in the non-haematopoietic transplant programme had been tested and, as a result, had not submitted any annual activity data to the HTA [(see shortfall against standard GQ5(b)].

The timetable for the site visit inspection was developed after consideration of the establishment's previous inspection report, communications with the HTA since the last inspection and annual activity data. The inspection included a visual inspection of the clinical consenting areas, apheresis unit, operating theatre complex, area for receipt, release processing and storage of samples, testing laboratory, and the Papworth Hospital consenting area and operating theatre complex. Documentation including policies, standard operating procedures, agreements, training records, meeting minutes, equipment records and examples of audits and quality incidents were reviewed. Roundtable discussions were held with relevant staff to review processing and storage records, to discuss the management of audits, incidents and risk assessments, and to discuss document control, labelling, contingency arrangements, recall and disposal. Interviews were held with the DI and the CLHC.

Audits of traceability were carried out:

1. A review of patient and processing records was undertaken for five haematological donations. This included: three autologous PBSC donations; one allogeneic sibling donation for both BM and PBSC; and one autologous paediatric BM donation. One of

the autologous PBSC donations had been consented at another hospital and the check boxes in the consent form had not been ticked, although the form was correctly signed and dated. No other discrepancies were noted.

2. Records for one clinical trial donation were reviewed. There was no evidence of the consent form within the patient records and the blood sample for serology testing was taken 18 days prior to procurement.
3. Electronic tracking records for the collection and receipt of blood samples for serology testing were reviewed for three haematological donations and the clinical trial described above. While blood samples were received into the PHE laboratory within the required timeframe for two of the haematological donations, the clinical trial blood sample was recorded as being received 22 hours after collection. No explanation for the delay was recorded. The allogeneic sibling donation blood sample was recorded as having been received in the testing laboratory at exactly the same time it was collected. No other discrepancies were noted (see *Advice*, item 5).
4. Processing/storage records for three of the haematological donations were compared to the electronic inventory spreadsheet. Cryovessel storage locations of all 12 bags of cryopreserved product and associated pilot vials on the spreadsheet correlated with the processing/storage record location.

Inspection findings

The HTA found the DI and the CLH to be suitable in accordance with the requirements of the legislation.

Compliance with HTA standards

Governance and Quality

Standard	Inspection findings	Level of shortfall
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.	A recent independent audit assessed compliance against the shortfalls identified from the last HTA inspection and areas for improvement identified at the last JACIE accreditation visit, rather than compliance against all applicable HTA standards, as required.	**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.	The establishment's donor selection procedure does not include questions to exclude risk of prion disease or donors who have ingested, or had an exposure to, a substance (such as cyanide, lead, mercury, gold) that may be transmitted to recipients in a dose that could endanger their health. See *Advice*, item 4	**Minor**
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.	The establishment's testing procedures for donors of cells for DLI, collected independently of PBSCs, and for the current clinical trial are not in line with Directions 002/2018 which stipulate that blood samples should be obtained on the day of collection, or if not possible within seven days post donation.	**Minor**
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.	The DI does not have practical oversight of donor blood samples used for serology testing as part of the separate non-haematopoietic transplant programme under a collaborative agreement, despite the fact that this activity is taking place under the establishment's licence. This issue is reflected in the lack of awareness of the number of samples tested on behalf of the separate non-haematopoietic transplant programme and the fact that this activity has not been reported to the HTA as part of the annual activity submission.	**Minor**
GQ8 Risk assessments of the establishment's practices and processes are completed regularly and are recorded and monitored appropriately.		
c) Staff can access risk assessments and are made aware of local hazards at training.	Although there is a detailed suite of risk assessments there is no evidence that these are readily available to staff.	**Minor**

Advice

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

No.	Standard	Advice
1.	C1(a)	The policies for the seeking of consent from both autologous and allogeneic donors (H/D001, H/P005) do not contain any information about the timing of the serological tests and the types of test, although this information is included in the consent forms. The DI is advised to consider updating the policies accordingly.

2.	GQ3(f)	The DI is advised to consider incorporating the following into the establishment's regulatory training programme: - Relevant parts of the 'Guide to Quality and Safety Assurance of Human Tissues and Cells for Patient Treatment'. - The Q&S Regulations Test Questions created by the HTA.
3.	GQ4(e)	The establishment maintains an electronic inventory/spreadsheet of all products that have been procured. The DI is advised to consider modifying the spreadsheet to allow inclusion of the SEC, when appropriate.
4.	GQ5(a)	The DI is also advised to consider adding a risk assessment of HEV transmission to the form on allogeneic donor selection.
5.	GQ5(b)	The establishment currently records when blood samples for serological testing are collected and when they are received at the testing laboratory. The DI is advised to consider a process that provides for full traceability of samples to be able to account for the location and storage of the samples should there be any delays in transfer, or inconsistencies in the recorded times.
6.	GQ6(d)	The SEC requirements vary depending upon the time when tissues and cells have been procured and stored. The establishment has been storing cells since 2010. The DI is advised to refer to the 'HTA guidance on coding and import regulations for tissues and cells in the human application sector' (page 9) for the different SEC requirements for each time period (before 29 October 2016, 29 October 2016-1 April 2018, after 1 April 2018).

Concluding comments

During the inspection, an area of good practice was noted:

- The establishment participates in quarterly meetings of the Human Tissue Management Committee, in which all of CUH FT DIs and the CLHC meet to discuss relevant governance and licensing issues.

There are a number of areas of practice that require improvement, including five minor shortfalls. The HTA has given advice to the DI with respect to the Consent and Governance and Quality standards.

The HTA requires that the DI 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: 24 July 2019

Report returned from DI: 30 July 2019

Final report issued: 22 August 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: 21 May 2020

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 002/2018 is included.
c) Information is available in suitable formats and there is access to independent interpreters when required.

d) There are procedures to ensure that information is provided to the donor or donor's family by trained personnel.
C3 Staff involved in seeking consent receive training and support in the implications and essential requirements of taking consent.
a) Staff involved in obtaining consent are provided with training on how to take informed consent in accordance with the requirements of the HT Act 2004 and Code of Practice on Consent.
b) Training records are kept demonstrating attendance at training on consent.

Governance and Quality

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

p) There are written agreements with third parties whenever an activity takes place that has the potential to influence the quality and safety of human tissues and / or cells.
q) There is a record of agreements established with third parties.
r) Third party agreements specify the responsibilities of the third party and meet the requirements set out in Directions 002/2018.
s) Third party agreements specify that the third party will inform the establishment in the event of a serious adverse reaction or event.
t) There are procedures for the re-provision of service in an emergency.
GQ2 There is a documented system of quality management and audit.
a) There is a quality management system which ensures continuous and systematic improvement.
b) There is an internal audit system for all licensable activities.
c) An audit is conducted in an independent manner at least every two years to verify compliance with protocols and HTA standards, and any findings and corrective actions are documented.
d) Processes affecting the quality and safety of tissues and / or cells are validated and undergo regular evaluation to ensure they continue to achieve the intended results.
GQ3 Staff are appropriately qualified and trained in techniques relevant to their work and are continuously updating their skills.
a) There are clearly documented job descriptions for all staff.
b) There are orientation and induction programmes for new staff.
c) There are continuous professional development (CPD) plans for staff and attendance at training is recorded.
d) There is annual documented mandatory training (e.g. health and safety and fire).
e) Personnel are trained in all tasks relevant to their work and their competence is recorded.
f) There is a documented training programme that ensures that staff have adequate knowledge of the scientific and ethical principles relevant to their work, and the regulatory context.
g) There is a documented training programme that ensures that staff understand the organisational structure and the quality systems used within the establishment.
h) There is a system of staff appraisal.
i) Where appropriate, staff are registered with a professional or statutory body.
j) There are training and reference manuals available.
k) The establishment is sufficiently staffed to carry out its activities.
GQ4 There is a systematic and planned approach to the management of records.
a) There are procedures for the creation, identification, maintenance, access, amendment, retention and destruction of records.

b) There is a system for the regular audit of records and their content to check for completeness, legibility and accuracy and to resolve any discrepancies found.
c) Written records are legible and indelible. Records kept in other formats such as computerised records are stored on a validated system.
d) There is a system for back-up / recovery in the event of loss of computerised records.
e) The establishment keeps a register of the types and quantities of tissues and / or cells that are procured, tested, preserved, processed, stored and distributed or otherwise disposed of, and on the origin and destination of tissues and cells intended for human application.
f) There are procedures to ensure that donor documentation, as specified by Directions 002/2018, is collected and maintained.
g) There is a system to ensure records are secure and that donor confidentiality is maintained in accordance with Directions 002/2018.
h) Raw data which are critical to the safety and quality of tissues and cells are kept for 10 years after the use, expiry date or disposal of tissues and / or cells.
i) The minimum data to ensure traceability from donor to recipient as required by Directions 002/2018 are kept for 30 years after the use, expiry or disposal of tissues and / or cells.
j) Records are kept of products and material coming into contact with the tissues and / or cells.
k) There are documented agreements with end users to ensure they record and store the data required by Directions 002/2018.
l) The establishment records the acceptance or rejection of tissue and / or cells that it receives and in the case of rejection why this rejection occurred.
m) In the event of termination of activities of the establishment a contingency plan to ensure records of traceability are maintained for 10 or 30 years as required.
GQ5 There are documented procedures for donor selection and exclusion, including donor criteria.
a) Donors are selected either by the establishment or the third party acting on its behalf in accordance with the criteria required by Directions 002/2018.
b) The testing of donors by the establishment or a third party on behalf of the establishment is carried out in accordance with the requirements of Directions 002/2018.
c) In cases other than autologous donors, donor selection is carried out by authorised personnel and signed and reviewed by a qualified health professional.
d) There is a system in place either at the establishment or at a third party acting on its behalf to record results of donor selection and associated tests.
e) Testing of donor samples is carried out using CE marked diagnostic tests.
f) Samples taken for donor testing are clearly labelled with the time and place the sample was taken and a unique donor identification code.

GQ6 A coding and records system facilitates traceability of tissues and / or cells, ensuring a robust audit trail.
a) There is a donor identification system which assigns a unique code to each donation and to each of the products associated with it.
b) An audit trail is maintained, which includes details of when the tissues and / or cells were acquired and from where, the uses to which the tissues and / or cells were put, when the tissues and / or cells were transferred elsewhere and to whom.
c) The establishment has procedures to ensure that tissues and / or cells imported, procured, processed, stored, distributed and exported are traceable from donor to recipient and vice versa.
d) The requirements of the Single European Code are adhered to as set out in Directions 002/2018.
GQ7 There are systems to ensure that all adverse events, reactions and/or incidents are investigated promptly.
a) There are procedures for the identification, reporting, investigation and recording of adverse events and reactions, including documentation of any corrective or preventative actions.
b) There is a system to receive and distribute national and local information (e.g. HTA regulatory alerts) and notify the HTA and other establishments as necessary of serious adverse events or reactions.
c) The responsibilities of personnel investigating adverse events and reactions are clearly defined.
d) There are procedures to identify and decide the fate of tissues and / or cells affected by an adverse event, reaction or deviation from the required quality and safety standards.
e) In the event of a recall, there are personnel authorised within the establishment to assess the need for a recall and if appropriate initiate and coordinate a recall.
f) There is an effective, documented recall procedure which includes a description of responsibilities and actions to be taken in the event of a recall including notification of the HTA and pre-defined times in which actions must be taken.
g) Establishments distributing tissue and / or cells provide information to end users on how to report a serious adverse event or reaction and have agreements with them specifying that they will report these events or reactions.
h) Establishments distributing tissues and / or cells have systems to receive notifications of serious adverse events and reactions from end users and notify the HTA.
GQ8 Risk assessments of the establishment’s practices and processes are completed regularly and are recorded and monitored appropriately.
a) There are documented risk assessments for all practices and processes.
b) Risk assessments are reviewed regularly, as a minimum annually or when any changes are made that may affect the quality and safety of tissues and cells.
c) Staff can access risk assessments and are made aware of local hazards at training.
d) A documented risk assessment is carried out to decide the fate of any tissue and / or cells stored prior to the introduction of a new donor selection criteria or a new processing step, which enhances the quality and safety of tissue and / or cells.

Premises, Facilities and Equipment

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

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 Human Tissue Act 2004, Human Tissue (Quality and Safety for Human Application) Regulations 2007 or the HTA Directions.

1. **Critical shortfall:**

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

   or

   A number of ‘major’ shortfalls, none of which is critical on its own, but viewed cumulatively represents a systemic failure and therefore is 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 straight away.

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 failure to carry out satisfactory procedures for the release of tissues and cells 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 by adversely affecting the quality and safety of the tissues and cells.

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 the proposed action plan the establishment will be notified of the follow-up approach the HTA will take.