Site visit inspection report on compliance with HTA minimum standards

Clinical Research Facility GMP Unit

HTA licensing number 22643

Licensed for the

- **procurement, processing and testing of human tissues and cells for human application under the Human Tissue (Quality and Safety for Human Application) Regulations 2007**

20-21 March 2018

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 the Clinical Research Facility GMP Unit (the establishment) had met the majority of the HTA's standards, six minor shortfalls were found in relation to: (i) incomplete recording of products and material coming into contact with tissues and cells; (ii) an absence of a documented plan for the contingency storage of records; (iii) an absence of risk assessments for procurement activities; (iv) inappropriate review periods for risk assessments; (v) an absence of risk assessments for procurement areas outside the CRF GMP Unit; and (vi) an absence of temperature monitoring of critical reagents in a procurement area outside the CRF GMP Unit.

Advice has been given relating to the Consent and Governance and Quality Systems standards, as well as advice on licence management.

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

The HTA's regulatory requirements

The HTA must assure itself that the Designated Individual (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.

'SLA' = Service level agreement; another establishment (licensed) carries out the activity on behalf of the establishment.

'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	Distribution
Other; Skin Biopsy (ATMP)	**E***		**TPA**	**SLA**
Progenitor Cell, Hematopoietic, Unspecified; Peripheral Blood	**E***	**E***	**TPA**	

Mononuclear Cells (PBMC)				
Progenitor Cell, Hematopoietic, Unspecified; Whole Blood	**E**		**TPA**	

Background to the establishment and description of inspection activities undertaken

This report refers to the activities carried out by the Clinical Research Facility Good Manufacturing Practice Unit (CRF GMP Unit; the establishment), which was issued an HTA licence in January 2013. This was the second HTA site visit inspection of the establishment (the last inspection was in March 2016). The current inspection was a routine one to assess whether the CRF GMP Unit is continuing to meet the HTA's standards.

The establishment is based in the National Institute of Health Research Biomedical Research Centre (NIHR BRC) on the 15th floor of the Tower Wing at Guy's Hospital, part of Guy's and St Thomas' NHS Foundation Trust. The establishment is involved in the manufacture of cell and gene therapies in clinical trials and as such has a licence from the Medicines and Healthcare products Regulatory Agency (MHRA) for the manufacture of Investigational Medicinal Products and Specials. Additional procurement activities under the licence have taken place in the Haematology Day Unit within the hospital (4th floor, Southwark Wing) and in the Nuclear Medicine Unit (ground floor, Borough Wing; see below).

The establishment is licensed under the Human Tissue (Quality and Safety for Human Application) Regulations 2007 (Q&S Regulations) for the procurement, processing and testing of tissues and cells for human application. Although licensed for testing, this activity is currently carried out under the terms of a third party agreement (TPA) with an unlicensed organisation based within the Trust ('testing centre'; see below).

The establishment is currently taking part in a clinical trial involving an advanced therapy medicinal product (ATMP) for autologous use (see below). The establishment has also been involved in a number of other clinical trials involving ATMPs which have now been completed and further ATMP trials work is planned (see below).

The DI is the Head of Advanced Therapy Production, the Corporate Licence Holder (CLH) is Guy's and St Thomas' NHS Foundation Trust and the CLH Contact (CLHC) is the Trust Chief Medical Officer. There are currently no Persons Designated (PDs) working under the licence (see *Advice*, item 1).

<u>Procurement</u>

The current ATMP clinical trial involves the procurement of whole blood within dedicated patient areas in the CRF GMP Unit. Previous ATMP clinical trials have involved the procurement of skin biopsies in the CRF GMP Unit, peripheral blood mononuclear cells (PBMCs) in the Haematology Day Unit and whole blood in the Nuclear Medicine Unit. In one forthcoming ATMP clinical trial, PBMCs will be procured in the Haematology Day Unit and, in a separate ATMP clinical trial, PBMCs will be procured under the terms of a TPA with a separate, unlicensed organisation and transported to the CRF GMP Unit for processing.

Donor selection (medical assessment) and the seeking of consent for procurement, including for mandatory serology tests, take place within dedicated patient areas in the CRF GMP Unit. Authorised staff working to a well-defined standard operating procedure (SOP) seek consent from the clinical trial participants. Staff are authorised to seek consent once they have completed an online training and competency assessment package. Patient information

sheets and consent forms are appropriate to each trial.

Samples for mandatory serology testing are taken up to 30 days prior to procurement and are repeated on the day of procurement (see *Advice*, item 5). Samples are transported by CRF GMP Unit staff to the testing centre.

The Haematology Day Unit contains four apheresis machines. These have been used in previous ATMP trials and will be used in a forthcoming ATMP trial [see shortfall against standard PFE1(a)]. Reagents and consumables for apheresis are stored in a secure storage area [see shortfall against standard PFE3(a)].

Processing

The processing facility is in the CRF GMP Unit. This consists of a clean room containing three aseptic laboratories. Each laboratory contains an isolator capable of maintaining a grade A processing environment against a background of grade D. Temperature-sensitive reagents and consumables are stored in a monitored and alarmed refrigerator.

Testing

The testing centre is a commercial provider of pathology services based within Guy's and St Thomas' NHS Foundation Trust. It is accredited by the United Kingdom Accreditation Service (UKAS) to International Organization for Standardization (ISO) standard 15189 (2012). Testing is carried out under the terms of a TPA. 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 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 CRF GMP Unit and Haematology Day Unit. Discussions and interviews were held with key staff and documentation was reviewed. Interviews were held with the DI, CLHC, apheresis nurse specialist, interim Head of Advanced Therapy Quality, two Clinical Research Fellows and a Consultant Medical Oncologist.

Audits of traceability were carried out:

- The electronic and paper records of donations to three clinical trials (two records for each trial: skin, PBMC, whole blood) were reviewed. The following information was cross-referenced: consent forms, collection checklists, product labels and results of microbiological and serological analysis. There were discrepancies noted [see shortfall against standard GQ4(j)].

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
GQ4 There is a systematic and planned approach to the management of records.		
j) Records are kept of products and material coming into contact with the tissues and / or cells.	During the inspection, it was noted that the batch and lot numbers of consumables and reagents coming into contact with tissues and cells were not recorded for any of the skin, PBMC or whole blood donations. These include: blood bags, tubes and syringes for whole blood collection, saline, gauze and universal tubes used for skin biopsies.	**Minor**
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.	There is no documented plan for the contingency storage of records of traceability and raw data in the event of termination of activities.	**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.	Although there is a detailed suite of risk assessments for the CRF GMP Unit, there are no risk assessments covering procurement activities outside the CRF GMP Unit to help assure the establishment that all possible risks have been considered. These include procurement activities carried out by third parties.	**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.	Risk assessments are currently reviewed every two years.	**Minor**

Premises, Facilities and Equipment

Standard	Inspection findings	Level of shortfall
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.	Although there is a risk assessment of the CRF GMP Unit to ensure that it is fit for purpose, there are no risk assessments of procurement areas outside the CRF GMP Unit in terms of safety, space and security to ensure that they are suitable. This includes third party premises.	**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.	During the inspection, it was noted that the storage temperature of Anticoagulant Citrate Dextrose Solution, Solution A (ACD-A) was not being monitored in the Haematology Day Unit.	**Minor**

Advice

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

No.	Standard	Advice
1.	N/A	The DI is advised to consider appointing a PD to assist them in their role as DI. Having a PD would ensure that serious adverse events and adverse reactions (SAEARs) are also reported on those occasions when the DI is absent. The HTA must be notified of such an appointment.
2.	C1(a), C3(a)	The DI is advised to consider including references to the new HTA's Code of Practice on 'Guiding Principles and the Fundamental Principle of Consent (Code A)' to the consent SOP and online training package.
3.	GQ1(c)	Joint governance meetings, involving DIs across the different sectors, are a feature in several other organisations that hold multiple HTA licences. The Trust is the CLH on four HTA licences and the University (King's College London) is CLH on two additional HTA licences within the Trust. Although there are frequent local meetings of the Quality Management Team, there are currently no meetings between DIs and individuals named on the licences described above. The DI and CLHCs are advised to consider setting up joint governance meetings involving staff on all of these licences as an opportunity for shared learning.
4.	GQ2(b)	The DI is advised to consider extending the audit schedule to include: (i) the areas where procurement takes place and (ii) procedural audits of the establishment's activities, to help assure the DI that the current practices being

		followed by establishment staff adequately reflect the content of SOPs.
5.	GQ5(b)	Donors of whole blood samples used as the starting material for ATMPs must have a serology sample for mandatory testing taken at the time of donation or, if not possible, within seven days post donation, in order to meet the requirements set out in Annex II of 2006/17/EC. In one of the completed clinical trials, it was noted that the serology sampling time point had been 30 days prior to donation. The DI is advised to ensure that serology sampling times are consistent with the requirements of the legislation for all clinical trials.

Concluding comments

During the inspection, areas of strength and good practice were noted:

- There is evidence of good teamwork and good lines of communication.
- There is a comprehensive online training and competency assessment package for staff who seek consent and carry out procurement under the licence. This package is also provided to third party consent seekers and procurers.
- 'Technical agreements' (TPAs) clearly delineate the responsibilities of each party in tabular form.
- There is a comprehensive Quality Manual highlighting a well-controlled Quality Management System.
- The establishment has good follow-up procedures for both internal and independent audits, with actions assigned to appropriate staff and findings distributed throughout the team.
- There is a detailed competency assessment training programme for all CRF GMP Unit staff, using a three-by-three matrix ('observing', 'being observed', 'being observed occasionally').
- The establishment has adopted the MHRA system of 'quality exception reports' (QERs) to cover all adverse events which take place. There are good follow-up procedures for all QERs with regular discussion at Quality Management Team meetings.

There are a number of areas of practice that require improvement, including six minor shortfalls. The HTA has given advice to the DI with respect to the Consent and Governance and Quality Systems standards, as well as advice on licence management.

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: 20 April 2018

Report returned from DI: 4 May 2018

Final report issued: 24 May 2018

Appendix 1: HTA standards

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

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

Consent

Standard
C1 Consent is obtained in accordance with the requirements of the HT Act 2004, the Human Tissue (Quality and Safety for Human Application) Regulations 2007 and as set out in the HTA's Codes of Practice.
a) If the establishment acts as a procurer of tissues and / or cells, there is an established process for acquiring donor consent which meets the requirements of the HT Act 2004 the Human Tissue (Quality and Safety for Human Application) Regulations 2007 (Q&S Regulations) and the HTA's Codes of Practice
b) If there is a third party procuring tissues and / or cells on behalf of the establishment the third party agreement ensures that consent is obtained in accordance with the requirements of the HT Act 2004, the Q&S Regulations and the HTA's Codes of Practice.
c) The establishment or the third party's procedure on obtaining donor consent includes how potential donors are identified and who is able to take consent.
d) Consent forms comply with the HTA Codes of Practice.
e) Completed consent forms are included in records and are made accessible to those using or releasing tissue and / or cells for a Scheduled Purpose.
C2 Information about the consent process is provided and in a variety of formats.
a) The procedure on obtaining consent details what information will be provided to donors. As a minimum, the information specified by Directions 003/2010 is included.
b) If third parties act as procurers of tissues and / or cells, the third party agreement details what information will be provided to donors. As a minimum, the information specified by Directions 003/2010 is included.
c) Information is available in suitable formats and there is access to independent interpreters when required.
d) There are procedures to ensure that information is provided to the donor or donor's family by trained personnel.
C3 Staff involved in seeking consent receive training and support in the implications and essential requirements of taking consent.
a) Staff involved in obtaining consent are provided with training on how to take informed consent in accordance with the requirements of the HT Act 2004 and Code of Practice on Consent.
b) Training records are kept demonstrating attendance at training on consent.

Governance and Quality

Standard
GQ1 All aspects of the establishment's work are supported by ratified documented policies and procedures as part of the overall governance process.
a) There is an organisational chart clearly defining the lines of accountability and reporting relationships.
b) There are procedures for all licensable activities that ensure integrity of tissue and / or cells and minimise the risk of contamination.
c) There are regular governance meetings, for example health and safety, risk management and clinical governance committees, which are recorded by agendas and minutes.
d) There is a document control system to ensure that changes to documents are reviewed, approved, dated and documented by an authorised person and only current documents are in use.
e) There are procedures for tissue and / or cell procurement, which ensure the safety of living donors.
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.
o) There is a complaints system in place.
p) There are written agreements with third parties whenever an activity takes place that has the potential to influence the quality and safety of human tissues and / or cells.
q) There is a record of agreements established with third parties.
r) Third party agreements specify the responsibilities of the third party and meet the requirements set out in Directions 003/2010.
s) Third party agreements specify that the third party will inform the establishment in the event of a serious adverse reaction or event.
GQ2 There is a documented system of quality management and audit.
a) There is a quality management system which ensures continuous and systematic improvement.
b) There is an internal audit system for all licensable activities.
c) An audit is conducted in an independent manner at least every two years to verify compliance with protocols and HTA standards, and any findings and corrective actions are documented.
d) Processes affecting the quality and safety of tissues and / or cells are validated and undergo

regular evaluation to ensure they continue to achieve the intended results.
GQ3 Staff are appropriately qualified and trained in techniques relevant to their work and are continuously updating their skills.
a) There are clearly documented job descriptions for all staff.
b) There are orientation and induction programmes for new staff.
c) There are continuous professional development (CPD) plans for staff and attendance at training is recorded.
d) There is annual documented mandatory training (e.g. health and safety and fire).
e) Personnel are trained in all tasks relevant to their work and their competence is recorded.
f) There is a documented training programme that ensures that staff have adequate knowledge of the scientific and ethical principles relevant to their work, and the regulatory context.
g) There is a documented training programme that ensures that staff understand the organisational structure and the quality systems used within the establishment.
h) There is a system of staff appraisal.
i) Where appropriate, staff are registered with a professional or statutory body.
j) There are training and reference manuals available.
k) The establishment is sufficiently staffed to carry out its activities.
GQ4 There is a systematic and planned approach to the management of records.
a) There are procedures for the creation, identification, maintenance, access, amendment, retention and destruction of records.
b) There is a system for the regular audit of records and their content to check for completeness, legibility and accuracy and to resolve any discrepancies found.
c) Written records are legible and indelible. Records kept in other formats such as computerised records are stored on a validated system.
d) There is a system for back-up / recovery in the event of loss of computerised records.
e) The establishment keeps a register of the types and quantities of tissues and / or cells that are procured, tested, preserved, processed, stored and distributed or otherwise disposed of, and on the origin and destination of tissues and cells intended for human application.
f) There are procedures to ensure that donor documentation, as specified by Directions 003/2010, is collected and maintained.
g) There is a system to ensure records are secure and that donor confidentiality is maintained in accordance with Directions 003/2010.
h) Raw data which are critical to the safety and quality of tissues and cells are kept for 10 years after the use, expiry date or disposal of tissues and / or cells.
i) The minimum data to ensure traceability from donor to recipient as required by Directions 003/2010

are kept for 30 years after the use, expiry or disposal of tissues and / or cells.
j) Records are kept of products and material coming into contact with the tissues and / or cells.
k) There are documented agreements with end users to ensure they record and store the data required by Directions 003/2010.
l) The establishment records the acceptance or rejection of tissue and / or cells that it receives and in the case of rejection why this rejection occurred.
m) In the event of termination of activities of the establishment a contingency plan to ensure records of traceability are maintained for 10 or 30 years as required.
GQ5 There are documented procedures for donor selection and exclusion, including donor criteria.
a) Donors are selected either by the establishment or the third party acting on its behalf in accordance with the criteria required by Directions 003/2010.
b) The testing of donors by the establishment or a third party on behalf of the establishment is carried out in accordance with the requirements of Directions 003/2010.
c) In cases other than autologous donors, donor selection is carried out by authorised personnel and signed and reviewed by a qualified health professional.
d) There is a system in place either at the establishment or at a third party acting on its behalf to record results of donor selection and associated tests.
e) Testing of donor samples is carried out using CE marked diagnostic tests.
f) Samples taken for donor testing are clearly labelled with the time and place the sample was taken and a unique donor identification code.
GQ6 A coding and records system facilitates traceability of tissues and / or cells, ensuring a robust audit trail.
a) There is a donor identification system which assigns a unique code to each donation and to each of the products associated with it.
b) An audit trail is maintained, which includes details of when the tissues and / or cells were acquired and from where, the uses to which the tissues and / or cells were put, when the tissues and / or cells were transferred elsewhere and to whom.
c) The establishment has procedures to ensure that tissues and / or cells imported, procured, processed, stored, distributed and exported are traceable from donor to recipient and vice versa.
GQ7 There are systems to ensure that all adverse events, reactions and/or incidents are investigated promptly.
a) There are procedures for the identification, reporting, investigation and recording of adverse events and reactions, including documentation of any corrective or preventative actions.
b) There is a system to receive and distribute national and local information (e.g. HTA regulatory alerts) and notify the HTA and other establishments as necessary of serious adverse events or reactions.
c) The responsibilities of personnel investigating adverse events and reactions are clearly defined.

d) There are procedures to identify and decide the fate of tissues and / or cells affected by an adverse event, reaction or deviation from the required quality and safety standards.
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.

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.
c) There are procedures for cleaning and decontamination.
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.
PFE4 Systems are in place to protect the quality and integrity of tissues and / or cells during transport and delivery to its destination.
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.
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.
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.