Licence application assessment (LAA) report on compliance with HTA licensing standards
LAA date: **28 June 2021 and 3 November 2021**

Royal Liverpool University Hospital

Proposed HTA licensing number 22686

Application for a licence under the Human Tissue (Quality and Safety for Human Application) Regulations 2007 (as amended)

Licensable activities applied to be carried out by the establishment
Proposed licensed activities

'E' = Establishment applied to be licensed to carry out this activity and will carry it out.

Site	Procurement	Processing	Testing	Storage	Distribution	Import	Export
Hub **Royal Liverpool University Hospital**	E		E			E	E

Tissue types applied to be authorised for licensed activities

Authorised = Establishment is authorised to carry out this activity and is currently carrying it out.

Applied to be authorised = Establishment to be authorised to carry out this activity and will currently be carrying it out.

Tissue Category; Tissue Type	Procurement	Processing	Testing	Storage	Distribution	Import	Export
Ocular, Cornea; Cornea						Applied to be Authorised	
Other, Limbal Stem Cells (ATMP)	Applied to be authorised		Applied to be authorised				Applied to be authorised

Summary of licence application assessment findings

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

The establishment has applied for a licence to carry out the import of corneal tissue and the procurement, testing and export of limbal stem cells. The import LAA was prioritised due to the establishment's urgent need for corneal tissues for patient treatment. The HTA was satisfied that systems were in place to offer the establishment an import licence with a corrective and preventative action (CAPA) plan to address six minor shortfalls. The import licence was issued in July 2021 with commitment from the DI that the minor shortfalls identified would be addressed within 3-4 months. The six minor shortfalls identified for the import activity were captured outside of this report.

The DI made a decision to address the shortfalls and complete the CAPA plan for the import activity before proceeding with the second part of the LAA which was carried out in November 2021 for the procurement, testing and export activities. Although the HTA found that Royal Liverpool University Hospital (the establishment) had met some of the HTA's standards in relation to these proposed activities, two major and 10 minor shortfalls were found against standards for Governance and Quality, and Premises, Facilities and Equipment.

The HTA is currently not satisfied that adequate systems are in place to offer the licence for the procurement, testing and export activities. This decision will be reviewed once the establishment has submitted evidence to demonstrate that, as a minimum, the major shortfalls detailed in the report below have been addressed.

Compliance with HTA standards
Major shortfalls

GQ3 Staff are appropriately qualified and trained in techniques relevant to their work and are continuously updating their skills.		
e) Personnel are trained in all tasks relevant to their work and their competence is recorded.	The staff have not been trained in all tasks relevant to their work.	**Major (cumulative)**
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.	The establishment does not have 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.	The establishment does not have a documented training programme that ensures that staff understand the organisational structure and the quality systems used within the establishment.	

GQ5 There are documented procedures for donor selection and exclusion, including donor criteria.		
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 001/2021.	The establishment has not provided assurance that the testing activities under the licence are carried out in accordance with HTA standards and the requirements of Directions 001/2021.	**Major**

Minor shortfalls

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.	The establishment does not have an organisational chart defining lines of accountability and reporting relationships for staff carrying out licensable activities.	**Minor**
s) Third party agreements specify that the third party will inform the establishment in the event of a serious adverse reaction or event.	The agreement with the manufacturer does not specify that the third party will notify the establishment within 24 hours of discovery in the event of a serious adverse reaction or event.	**Minor**

GQ2 There is a documented system of quality management and audit.		
a) There is a quality management system which ensures continuous and systematic improvement.	The establishment does not currently have a quality manual in place.	**Minor**
b) There is an internal audit system for all licensable activities.	There is no internal audit schedule in place for all licensable activities.	**Minor**

GQ4 There is a systematic and planned approach to the management of records.		
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.	The establishment does not have procedures in place to ensure that raw data is retained for 10 years after the use, expiry date or disposal of tissues and / or cells.	**Minor**
i) The minimum data to ensure traceability from donor to recipient as required by Directions 001/2021 are kept for 30 years after the use, expiry or disposal of tissues and / or cells.	The establishment does not have procedures in place to retain the minimum data needed to ensure traceability from donor to recipient for 30 years after the use, expiry date or disposal of tissues and / or cells.	**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.	The establishment does not have a contingency plan in place to ensure raw data and traceability records are retained for 10 or 30 years 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.	The establishment does not have risk assessments in place for all practices and processes.	**Minor**

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.	A risk assessment has not been completed of the premises to ensure they are fit for purpose.	**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's procedures do not specify the manufacturer's recommended temperature range for the storage of the kits prior to procurement.	**Minor**

Advice

The HTA advises the proposed DI to consider the following to further improve practice:

Number	Standard	Advice
1.	GQ2c	The DI is advised to confirm plans to conduct independent audits every two years as current plans have not been finalised.
2.	GQ4b	The DI is advised to incorporate into the internal audit schedule a regular audit of records and their content to check for completeness, legibility and accuracy and to resolve any discrepancies found.
3.	-	The DI is advised to consider appointing a Persons Designated (PD) to support him in their role as the DI. The PD can ensure serious adverse events and adverse reactions (SAEARs) are reported to the HTA on those occasions when the DI is absent. The DI must notify the HTA of the addition of PDs to the licence.

Background

Royal Liverpool University Hospital is a regional centre for corneal transplantation and has applied to import corneal tissue from a third country supplier for human application.

The establishment has also applied to carry out the procurement, testing and export of limbal stem cells. These activities are linked to the treatment which is offered to adult patients with unilateral or bilateral, moderate to severe limbal stem cell deficiency due to physical or chemical ocular burns. Limbal stem cells are procured as the starting material for an Advanced Therapy Medicinal Product (ATMP). The patients will be identified and consented for treatment at St Paul's Eye Unit. The donor blood samples are tested for mandatory serology markers less than 30 days before procurement, and on the day of procurement at a laboratory working under the authority of the establishment's licence. The following biological tests are performed for donors: HIV 1 & 2, Hepatitis A, Hepatitis B, Hepatitis C, Syphilis, Human T Lymphotropic Virus I (HTLV-1), Human West Nile virus

and Sars-Cov-2.

The manufacturer provides the biopsy collection kit before the procurement event. The collection tube is accompanied by the transport medium, documentation, instructions and the materials for the subsequent shipment of the biopsy to the manufacturer. An additional collection tube is provided in the kit as a contingency. The limbal stem cells are packaged and released by trained staff following the establishment's procedures, and sent to the manufacturer in Italy. The ATMP is returned to the patient for an autologous treatment. The establishment intends to use the checklist and forms provided by the manufacturer which are attached to the educational manual, in addition to the establishment's own documented procedures.

The DI is a Consultant Ophthalmologist and Professor at the University of Liverpool who is responsible for maintaining oversight of the licensable activities. A number of staff will carry out licensable activities, including a second Consultant Ophthalmologist who also performs surgery, the Liverpool Eye Donation Centre (LEDC) Manager, corneal nursing staff and theatre staff.

Description of activities undertaken during licence application assessment

The HTA's regulatory requirements are set out in Appendix 1. The Regulation Manager covered the following areas during the assessment:

Documentation was reviewed relating to the licensable activities. This included policies and procedures, agreements with third parties, risk assessments, patient information leaflets and the manufacturer's educational manual. The HTA carried out the licence application assessments remotely in the presence of the LEDC Manager and the DI.

Report sent to proposed DI for factual accuracy: 29 November 2021

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

Final report issued: 15 December 2021

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: 14 June 2022

Appendix 1: The HTA's regulatory requirements

The HTA must assure itself that the DI, Licence Holder, 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 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.

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 (as amended), 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 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:

   - A notice of proposal being issued to revoke the licence;
   - 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;
   - A notice of suspension of licensable activities;
   - Additional conditions being proposed, or;
   - 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 (as amended) 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 the final inspection report. Establishments 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, or;
- follow up at next routine site-visit inspection.

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

Appendix 3: HTA standards

The HTA standards applicable to this establishment are shown below. Individual standards which are not applicable to this establishment have been excluded.

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

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
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 001/2021 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.
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.
n) The establishment ensures imports from non-EEA states meet the standards of quality and safety set out in Directions 001/2021.
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 001/2021.
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.
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 001/2021, is collected and maintained.
g) There is a system to ensure records are secure and that donor confidentiality is maintained in accordance with Directions 001/2021.
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 001/2021 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.
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 001/2021.

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 001/2021.
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 UKCA or CE marked diagnostic tests, in line with the requirements set out in Directions 001/2021.
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.
a) Tissues and / or cells stored in quarantine are stored separately from tissue and / or cells that have been released from quarantine.
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 001/2021.
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 001/2021.
j) Shipping packaging containing tissues and / or cells is labelled with the information required by Directions 001/2021.
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.