Site visit inspection report on compliance with HTA licensing standards
Inspection date: **11-12 September 2019**

King's College Hospital

HTA licensing number 11006

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

and

Licensed under the Human Tissue Act 2004

Licensable activities carried out by the establishment
'E' = Establishment is licensed to carry out this activity and is currently carrying it out.
'TPA' = Third party agreement; the establishment is licensed for this activity but another establishment (not licensed by the HTA) carries out the activity on their behalf.

Licensed activities – Human Tissue (Quality and Safety for Human Application) Regulations 2007 (as amended)

Site	Procurement	Processing	Testing	Storage	Distribution	Import	Export
King's College Hospital	E	E	TPA	E	TPA		

Tissue types authorised for licensed activities – Human Tissue (Quality and Safety for Human Application) Regulations 2007 (as

amended)

Tissue Category; Tissue Type	Procurement	Processing	Testing	Storage	Distribution	Import	Export
Progenitor Cell, Haematopoietic, PBSC; PBSC	Authorised	Authorised	Authorised TPA	Authorised	Authorised TPA		
Progenitor Cell, Haematopoietic, Bone Marrow	Authorised	Authorised	Authorised TPA	Authorised	Authorised TPA		
Progenitor Cell, Haematopoietic, Cord Blood	Authorised	Authorised	Authorised TPA	Authorised	Authorised TPA		
Mature Cell, T cell	Authorised	Authorised	Authorised TPA	Authorised	Authorised TPA		

Licensed activities – Human Tissue Act 2004

Area	Storage of relevant material which has come from a human body for use for a scheduled purpose
King's College Hospital	Licensed

Summary of inspection findings

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

Although the HTA found that King's College Hospital (the establishment) had met the majority of the HTA's standards, four minor shortfalls were found against the standards for Governance and Quality. The shortfalls relate to the independent audit, the regular audit of records, the donor selection criteria and the testing of donors.

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.

Since the last inspection the establishment has undertaken the procurement and processing of peripheral blood mononuclear cells as a starting material for Advanced Therapy Medicinal Products (ATMP) manufacture, without prior notification to the HTA. The HTA considers this a breach of the standard condition of the establishment's licence, which requires it to seek approval from the HTA prior to it procuring a new type of tissue and/or cells. The HTA will consider the need for regulatory action in relation to this matter separately to the inspection findings reported below.

Compliance with HTA standards

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

Minor Shortfalls

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.	Although an independent audit was carried out in 2019, the audit did not include all applicable standards. For example, a considerable number (>20) of the Governance and Quality standards, and Premises, Facilities and Equipment standards were not audited.	**Minor**
GQ4 There is a systematic and planned approach to the management 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.	The establishment does not conduct a regular audit of records to check for completeness, legibility and accuracy.	**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 003/2010.	The donor questionnaire does not contain questions about organ transplantation, xenografts, and ingestion of, or exposure to, a substance (such as cyanide, lead, mercury, gold) that may be transmitted to recipients in a dose that could endanger their health.	**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 003/2010.	Donors that undergo procurement of cells for donor lymphocyte infusions (DLI) independently of any other tissue/cells, are tested within 30 days prior to the procurement. However, the mandatory testing on the day of procurement (or up to seven days post donation) is not carried out.	**Minor**

The establishment is also licensed for the storage of relevant material for use for a scheduled purpose under the Human Tissue Act 2004. The establishment does not currently store relevant material. Therefore, the applicable HTA standards were not audited during this

inspection.

The HTA requires the DI to submit a completed corrective and preventative action (CAPA) plan setting out how the shortfalls will be addressed, 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.

DI and CLH/LH suitability

The HTA found the Designated Individual (DI) and the Licence Holder (LH) to be suitable in accordance with the requirements of the legislation. However, since the last inspection the establishment has undertaken the procurement and processing of peripheral blood mononuclear cells (PBMC) as a starting material for ATMP manufacture, without prior notification to the HTA. The HTA considers this a breach of the standard condition of the establishment's licence, which requires it to seek approval from the HTA prior to it procuring a new type of tissue and/or cells. The HTA will consider the need for regulatory action in relation to this matter separately to the inspection findings reported below.

Advice

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

Number	Standard	Advice
1.	GQ1c	During the inspection, it took several members of staff to locate the SEC-DI for one starting material. The DI is advised to ensure all staff working under the licence are aware where the SEC-DI is recorded and are able to access it.
2.	GQ1s	The cell processing team holds weekly, operational meetings, which are minuted. A recent product supply issue that prompted changes in processing procedures was apparently discussed amongst the team. However, this was not captured in the meeting minutes. The DI is advised to ensure that the content of the meetings is accurately documented in the minutes.
3.	GQ6d	The agreement between the establishment and one of the ATMP manufacturers documents the reciprocal duty of both parties to notify each other of incidents. The DI is advised to review the agreement so that the

		manufacturer shall notify the DI of any incidents detected at later stages of the manufacturing process, which may have their root cause in events that took place under the establishment's licence.

Background

The establishment has been licensed by the HTA since August 2006 under the Human Tissue (Quality and Safety for Human Application) Regulations 2007 (as amended). The establishment carries out procurement, donor testing, processing, storage and distribution of peripheral stem cells, bone marrow and peripheral blood lymphocytes for donor lymphocyte infusions (DLI). Umbilical cord blood is not procured on-site but is sent to the establishment for processing from another HTA-licensed establishment. The establishment has not processed cord blood for over one year. In 2018, the establishment began the procurement, processing and donor testing of PBMC, which are used as starting material for two ATMPs.
The testing of donors and microbiological testing of cell products is carried out by two accredited laboratories under the terms of appropriate third party agreements.
This was the seventh inspection of the establishment. The most recent previous inspection took place in September 2017.
Since the previous inspection, a change of DI took place in 2018. In the same year, the processing activities were moved to the newly built Cellular Therapy Unit (CTU).

Description of inspection activities undertaken

The HTA's regulatory requirements are set out in Appendix 1. The inspection team covered the following areas during the inspection:

Standards assessed against during inspection
There are 121 number of standards in the Human Application sector of which 116 were assessed. Standards GQ1f, GQ1n and PFE1d were not applicable, and standards GQ3c and GQ8d were not assessed.

Review of governance documentation
The inspection included a review of documentation relevant to the establishment's licensable activities. This included policies and procedural documents, contracts for servicing of equipment and records of servicing, temperature monitoring for the storage units, agreements with third parties, patient records, including records for procurement, processing and testing, meeting minutes, incidents, adverse events, audits, risk assessments, and staff training records.

Visual inspection

The inspection included a visual inspection of the apheresis suite, the cell quality control laboratory, the CTU, the cryostore, the clinical consent area, and the in-house virology and microbiology testing laboratory.

Audit of records

The procurement and processing records were audited for the following cells/tissue donors:

- an allogenic unrelated peripheral stem cell donor
- an autologous peripheral stem cell donor
- a peripheral stem cell sibling donor and corresponding transplant record for the recipient. The transplant record of the sibling recipient was not completed correctly.
- an allogenic unrelated bone marrow donor (procurement record only)
- a DLI donor and the corresponding infusion record for the recipient
- two donors who donated PBMC as ATMP starting material for autologous treatment.

The serology results of four of the donors were traced in the testing laboratory and no discrepancies were found.

Meetings with establishment staff

The inspection included interviews with the Processing Facility Director (who is the DI) and the CLHc who is the Executive Medical Director of the hospital, and discussions with the Collection Facility Director, Clinical Quality Manager, Collection Facility Quality Manager, Bone Marrow Collection Facility Medical Director, Clinical Quality Manager, the CTU Quality Director, the Processing Facility Quality Manager, the Clinical Director of the Department of Haematological Medicine, the Director of Transplantation, and the Quality Manager of the in-house testing laboratory.

Report sent to DI for factual accuracy: 8th October 2019

Report returned from DI: 23rd October 2019

Final report issued: 25th October 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: 24 April 2020

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 (HT Act), Human Tissue (Quality and Safety for Human Application) Regulations 2007, or associated Directions.

1. **Critical shortfall:**

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

   Or

   A shortfall which poses a significant risk to human safety and/or dignity or is a breach of the HT Act or associated Directions,

   Or

   A number of 'major' shortfalls, none of which are 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
   - Directions being issued requiring specific action to be taken straightaway

2. Major shortfall:

A non-critical shortfall.

A shortfall in the carrying out of licensable activities which poses an indirect risk to the safety of a donor or a recipient

or

A shortfall in the establishment's quality and safety procedures which poses an indirect risk to the safety of a donor or a recipient;

or

A shortfall which indicates a major deviation from the Human Tissue (Quality and Safety for Human Application) Regulations 2007 or the HTA Directions;

or

A shortfall which indicates a breach in the relevant Codes of Practice, the HT Act and other relevant professional and statutory guidelines;

or

A shortfall which indicates a failure to carry out satisfactory procedures or a failure on the part of the designated individual to fulfil his or her legal duties;

or

A combination of several 'minor' shortfalls, none of which is major on its own, but which, viewed cumulatively, could constitute a major shortfall.

In response to a major shortfall, an establishment is expected to implement corrective and preventative actions within 1-2 months of the issue of the final inspection report. Major shortfalls pose a higher level of risk and therefore a shorter deadline is given, compared to minor shortfalls, to ensure the level of risk is reduced in an appropriate timeframe.

3. Minor shortfall:

A shortfall which cannot be classified as either critical or major and, which can be addressed by further development by the

establishment.

This category of shortfall requires the development of a corrective action plan, the results of which will usually be assessed by the HTA either by desk based review or at the time of the next inspection.

In response to a minor shortfall, an establishment is expected to implement corrective and preventative actions within 3-4 months of the issue of the final inspection report.

Follow up actions

A template corrective and preventative action plan will be sent as a separate Word document with 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
- follow up at next routine site-visit inspection.

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