Site visit inspection report on compliance with HTA licensing standards

University of Cambridge – Downing Site

HTA licensing number 12196

Licensed under the Human Tissue Act 2004 for the

- **storage of relevant material which has come from a human body for use for a scheduled purpose**

6 and 7 November 2018

Summary of inspection findings

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

Although the HTA found that The University of Cambridge- Downing Site had met the majority of the HTA's standards, five minor shortfalls were found. The shortfalls were related to risk assessments (GQ6(a)), standardisation of traceability systems between the different departments (T1(c) and T2(b)) and maintenance and monitoring of temperature controlled freezer storage (PFE2(c) and PFE3(a)).

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

The HTA's regulatory requirements

Prior to the grant of a licence, the HTA must assure itself that the Designated Individual is a suitable person to supervise the activity authorised by the licence and that the premises are suitable for the activity.

The statutory duties of the Designated Individual are set down in Section 18 of the Human Tissue Act 2004. They are to secure that:

- the other persons to whom the licence applies are suitable persons to participate in the carrying-on of the licensed activity;
- suitable practices are used in the course of carrying on that activity; and
- the conditions of the licence are complied with.

Its programme of site visit inspections to assess compliance with HTA licensing standards is one of the assurance mechanisms used by the HTA.

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. They are grouped under four headings:

- consent
- governance and quality systems
- traceability
- premises facilities and equipment.

This is an exception-based report: only those standards that have been assessed as not met are included. Where the HTA determines that there has been a shortfall against a standard, 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 provided.

HTA inspection reports are published on the HTA's website.

Background to the establishment

University of Cambridge- Downing site (the establishment) comprises a hub and three satellite sites, all part of the University of Cambridge. The establishment is licensed by the HTA under the Human Tissue Act 2004 (HT Act) for the storage of relevant material which has come from a human body, for a scheduled purpose.

The establishment has been licensed since July 2007 and was last inspected in September 2010. This report describes the second routine inspection of the establishment, the hub and its associated satellite sites.

The DI supervising activities taking place under the licence is the Director of Health and Safety (and Governance and Compliance) for the University of Cambridge, the Corporate Licence Holder (CLH) is the University of Cambridge and the CLH contact (CLHc) is the Biological and General Safety Advisor for the University of Cambridge. The DI and CLHc oversee all licensable activities and are actively, and closely, engaged with all the research groups.

The establishment is organised as a central hub facility with three satellites sites. Storage of relevant material occurs in eight departments distributed throughout the four sites (see Table 1 below), with each department containing one to nine research groups that work with relevant material. Each department has a named individual as Person Designated (PD) overseeing all licensable activity in the department and regularly meeting with the DI, CLHc and other PDs. Each group sources relevant material through direct recruitment or through collaborators, either under ethics approval from a recognised NHS Research Ethics Committee (REC), from a research tissue bank (RTB), or from abroad. The majority of relevant material routinely stored under the HTA licence is imported from abroad (including European collaborators, groups in the United States, and in Africa and Asia) or is stored at the Centre for Trophoblast Research (CTR) RTB within the Department of Physiology, Development & Neuroscience. All imported tissue is either accompanied by a completed consent form or a truncated consent form and an accompanying documented agreement providing an assurance that consent has been taken. At the time of the inspection, two departments - the Wellcome Trust Medical Research Council Stem Cell Institute (Gleeson Building) and the Department of Biochemistry - had no material stored under the HTA licence and were not inspected during the site visit.

Table 1. List of licensed departments at the hub and satellite sites.

Downing site (Hub)	Old Addenbrooke's (Satellite)	New Museums (Satellite)	West Cambridge (Satellite)
Department of Pathology	Wellcome Trust Medical Research Council Stem Cell Institute (Gleeson Building)	Department of Zoology	Department of Veterinary Medicine
Department of Physiology, Development & Neuroscience (CTR RTB)	Department of Archaeology		Department of Physics
Department of Biochemistry	Gurdon Institute		Department of Chemical Engineering & Biotechnology

Samples across the establishment originate from adults, children and foetuses, and include both tissue and bodily fluids. Originating from both living and deceased donors, relevant material includes formalin-fixed material (e.g. embryos), formalin-fixed, paraffin wax-embedded blocks and sections on glass slides, isolated cellular preparations (e.g. peripheral blood mononuclear cells), bones and teeth, fresh frozen tissue (e.g. Liver and Brain) and frozen tissue sections on glass slides. Material also includes tissue homogenate and bodily fluids including breast milk, faecal tissue, cerebral spinal fluid, urine, whole blood, saliva.

The establishment has generated example standardised documents (e.g. consent forms, risk assessments, SOPs) and individual groups may adapt the documents for their own use. A bespoke sample management system/sample tracker has been created by the University and has been adopted by most groups. After review, groups with existing sample tracking systems and large existing collections/datasets where it has been determined that the existing data would be problematic to transfer to the new system, continue to use their existing system. This has been assessed on a case-by-case basis and it is expected that any new groups joining the establishment will use the bespoke system. The bespoke system allows for all pertinent information to be recorded for received, stored and used/disposed samples, although it has been used inconsistently (see shortfall against T2(b)).

Samples are stored in secure areas, accessible to trained establishment staff. However, in several of the departments this includes staff who do not normally work with human tissue and do not have any HTA-related training, (see *Advice*, item 8). Samples are stored in liquid nitrogen (LN2) storage vessels/cryovessels (both liquid and vapour phase), in freezers (-80ºC

and -20ºC) and in secured ambient temperature storage. There is ample freezer space as contingency.

Some, but not all, storage facilities are linked to temperature monitoring units using a commercially available web-based system with a wireless call out system (see shortfall against PFE2(c)). Temperature excursions outside of the set ranges trigger local alarms, and in the case of the -80ºC freezers, there is an automated call out system. However, only one of the groups inspected reported that they routinely challenged the freezer monitoring and alarms, although the system was subject to regular maintenance (see shortfall against PFE2(c)). The majority of freezers and LN2 storage vessels were labelled as containing human tissue, with contact details for the responsible individuals for the units, and steps to be taken when the audible alarm sounds.

Description of inspection activities undertaken

The timetable for the site visit was developed after consideration of the establishment's previous inspection report, compliance update information and communications with the HTA. The inspection included a visual inspection of areas where licensable activities were undertaken in all eight departments currently working with relevant material under the HTA licence. Interviews were held with the DI and CLHc, and roundtable discussions held with PDs and staff at each department. In addition to a review of documentation, sample traceability audits were carried out.

Traceability audits were performed on samples contained within 13 groups in the eight departments inspected (82 samples in total). The samples were randomly selected from each sample collection and location and labelling details were compared against electronic and paper records. Samples were audited from storage locations to records and from records to storage locations. Where available, completed consent forms were reviewed for each sample, or documented agreements with third parties were reviewed to ensure appropriate consent was in place. The majority of groups utilised the University bespoke sample management system, while several groups with large data sets continued to use their pre-existing systems. There were several discrepancies noted (see shortfall against T1(c)).

Inspection findings

The HTA found the Licence Holder and the Designated Individual suitable in accordance with the requirements of the legislation.

Compliance with HTA standards

Governance and Quality

Standard	Inspection findings	Level of shortfall
GQ6 Risk assessments of the establishment's practices and processes are completed regularly, recorded and monitored		
a) There are documented risk assessments for all practices and processes requiring compliance with the HT Act and the HTA's Codes of Practice.	Example risk assessments are provided by the establishment, but individual groups generate their own specific risk assessments. While many risk assessments were in place, some groups did not have risk assessments for all relevant practices and processes. These included, but were not limited to: There was no risk assessment for the storage of samples for DNA extraction in an unmonitored -20ºC freezer in the Dept. of Pathology. There was no risk assessment related to the manual transport, by staff in the Dept. of Pathology, of relevant material from a collaborator's laboratory. There were no risk assessments related to the decision to not maintain service contracts for the -80ºC freezers used in two departments at the establishment.	**Minor** ***Prior to the final report being issued the DI submitted evidence of the actions taken in relation to the shortfall. The HTA has assessed this evidence as satisfactory and considers this standard to be met.***

Traceability

Standard	Inspection findings	Level of shortfall
T1 A coding and records system facilitates the traceability of bodies and human tissue, ensuring a robust audit trail		
c) An audit trail is maintained, which includes details of: when and where the bodies or tissue were acquired and received; the consent obtained; all sample storage locations; the uses to which any material was put; when and where the material was transferred, and to whom.	During the sample traceability audit it was noted that one of the groups in Pathology were not able to provide records of the details of when tissue had been acquired and received, for a set of cervical blocks (10) and slides (10). In addition, staff were unable to locate, or provide records of a slide identified during the audit of cervical samples, resulting in a loss of traceability.	**Minor** ***Prior to the final report being issued the DI submitted evidence of the actions taken in relation to the shortfall. The HTA has assessed this evidence as satisfactory and considers this standard to be met.***
T2 Bodies and human tissue are disposed of in an appropriate manner		
b) The date, reason for disposal and the method used are documented.	The bespoke sample management system, provided by the University, and in use by most groups, allows for the date and method of disposal, but does not specifically record the reason. Some individuals record the reason in the 'free text' methods box but there is a lack of consistency in practice. See *Advice*, item 7	**Minor** ***Prior to the final report being issued the DI submitted evidence of the actions taken in relation to the shortfall. The HTA has assessed this evidence as satisfactory and considers this standard to be met.***

Premises, Facilities and Equipment

Standard	Inspection findings	Level of shortfall
PFE2 There are appropriate facilities for the storage of bodies and human tissue		
c) Storage conditions are monitored, recorded and acted on when required.	During the inspection, it was noted that the -80ºC freezer in the Department of Physiology, Development and Neuroscience was not temperature monitored, although it was alarmed. One of the groups in the Department of Pathology maintained a -20ºC freezer containing tissue samples intended for eventual DNA extraction; the freezer was not temperature monitored and had only a local 'audible' alarm system. The Department of Pathology stored all LN2 samples in a room shared by the department; while fitted with liquid level detectors, none of the units were temperature monitored. The majority of groups across the establishment do not routinely challenge the alarm systems, although they are maintained under a service contract.	**Minor** ***Prior to the final report being issued the DI submitted evidence of the actions taken in relation to the shortfall. The HTA has assessed this evidence as satisfactory and considers this standard to be met.***
PFE3 Equipment is appropriate for use, maintained, validated and where appropriate monitored		
a) Equipment is subject to recommended calibration, validation, maintenance, monitoring, and records are kept.	Two of the departments inspected do not maintain their -80ºC freezers under a preventative maintenance service contract. See *Advice*, item 5 The Department of Veterinary Medicine maintain samples in vapour phase LN2 storage. At the inspection the oxygen depletion monitor was not working, however Health and Safetly colleagues were consulted and the establishment instituted an interim'buddy' system when accessing the storage facility, in order to minimise risk.	**Minor** ***Prior to the final report being issued the DI submitted evidence of the actions taken in relation to the shortfall. The HTA has assessed this evidence as satisfactory and considers this standard to be met.***

Advice

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

No.	Standard	Advice
1.	C2(c)	Establishment staff undertake online, or face-to-face training on the relevant regulatory requirements for consent. The DI is advised to implement a system to ensure that appropriate staff undertake regular refresher training and to maintain a centralised list of all individuals who have undertaken consent training.
2.	GQ1(a)	The Department of Veterinary Medicine is undertaking a trial with fully anonymised volunteers. As findings of potential medical importance to donors may be made while undertaking human tissue research, including 'incidental findings' beyond the aims of the research, the PI may wish to consider options to manage any such findings with potential clinical relevance, so that they may be fed back to the volunteers. The Medical Research Council (MRC) and Wellcome Trust have published a 'Framework on the feedback of health-related findings in research' which provides further guidance on the approaches that may be taken.
3.	GQ2(a)	The CLHc undertakes both annual and scheduled audits of each department. Other departments, such as the Department of Chemical Engineering & Biotechnology, also undertake internal reviews and audits of their documents and tissue. The DI is advised to ensure that these audits are formally documented.
4.	GQ2(a)	The CLHc undertakes regular audits of each group working under the licence. The DI is advised to consider a system where groups undertake audits of each other as this would facilitate the sharing of good practice between the different groups.
5.	GQ6(a)	Due to the large number of -80ºC freezers across the establishment, and the cost involved in regular maintenance, two of the departments have made the decision to not have service contracts for their -80ºC freezers. If a unit fails they transfer the material to a 'back-up' -80ºC freezer and either repair or replace the failed unit. The DI is advised to formally document this process and ensure all appropriate risks have been considered.
6.	T1(b)	The majority of relevant material held at the establishment is under approval from a recognised REC. The DI is advised to maintain a list of all REC approved studies, including when they will come to an end, in order to provide an assurance that at the end of studies relevant material is either maintained under the governance of the HTA licence or disposed of appropriately.
7.	T1(c)	The bespoke sample management system provided by the University allows individuals to add 'free text' in some fields. The DI is advised to consider systems that would standardise the response in these fields and ensure that all individuals provide consistent information.
8.	PFE1(b)	Most groups store 'relevant material' in areas accessible to researchers who do not work with human material. The DI is

		advised to ensure that all staff that have access to 'relevant material' undergo basic training related to the Human Tissue Act 2004 (the HT Act) as part of their induction training. This will ensure that staff are aware of the requirements under the HT Act and the need to limit access to the 'relevant material'.
9.	PFE2(c)	The DI is advised to consider implementing a system where the temperature plots from the monitoring system are regularly reviewed by all groups, as this may indicate a potential failure of the freezers before it occurs.

Concluding comments

The DI and CLHc are actively involved and engaged with each of the departments under the licence. The CLHc has developed an extensive set of generic documents (in a Quality Manual) that may be adapted by each group, covering risk assessments, SOPs and consent documentation. She undertakes an annual audit of each department, together with a number of audits throughout the year (which are formally recorded with CAPAs). Follow-up actions noted during the inspection showed how this governance approach, and open conversation with staff, had helped improve individual department compliance against the HTA standards. There are a number of areas of practice that require improvement, including five minor shortfalls.

The HTA requires the Designated Individual 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.

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: 05 December 2018

Report returned from DI: 11 January 2019

Final report issued: 15 January 2019

Completion of corrective and preventative actions (CAPA) plan

Based on information provided, the HTA is satisfied that the establishment has completed the agreed actions in the CAPA plan and in doing so has taken sufficient action to correct all shortfalls addressed in the Inspection Report.

Date: 28 January 2019

Appendix 1: HTA standards

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

Consent standards
C1 Consent is obtained in accordance with the requirements of the Human Tissue Act 2004 (HT Act) and as set out in the code of practice
a) Consent procedures are documented and these, along with any associated documents, comply with the HT Act and the HTA's Codes of Practice. b) Consent forms are available to those using or releasing relevant material for a scheduled purpose. c) Where applicable, there are agreements with other parties to ensure that consent is obtained in accordance with the requirements of the HT Act and the HTA's Codes of Practice. d) Written information is provided to those from whom consent is sought, which reflects the requirements of the HT Act and the HTA's Codes of Practice. e) Language translations are available when appropriate. f) Information is available in formats appropriate to the situation.
C2 Staff involved in seeking consent receive training and support in the essential requirements of taking consent
a) There is suitable training and support of staff involved in seeking consent, which addresses the requirements of the HT Act and the HTA's Codes of Practice. b) Records demonstrate up-to-date staff training. c) Competency is assessed and maintained.

Governance and quality system standards
GQ1 All aspects of the establishments work are governed by documented policies and procedures as part of the overall governance process
a) Ratified, documented and up-to-date policies and procedures are in place, covering all licensable activities. b) There is a document control system. c) There are change control mechanisms for the implementation of new operational procedures. d) Matters relating to HTA-licensed activities are discussed at regular governance meetings, involving establishment staff. e) There is a system for managing complaints.
GQ2 There is a documented system of audit
a) There is a documented schedule of audits covering licensable activities. b) Audit findings include who is responsible for follow-up actions and the timeframes for completing these.

GQ3 Staff are appropriately qualified and trained in techniques relevant to their work and are continuously updating their skills
a) Qualifications of staff and all training are recorded, records showing attendance at training.
b) There are documented induction training programmes for new staff.
c) Training provisions include those for visiting staff.
d) Staff have appraisals and personal development plans.
GQ4 There is a systematic and planned approach to the management of records
a) There are suitable systems for the creation, review, amendment, retention and destruction of records.
b) There are provisions for back-up / recovery in the event of loss of records.
c) Systems ensure data protection, confidentiality and public disclosure (whistleblowing).
GQ5 There are systems to ensure that all adverse events are investigated promptly
a) Staff are instructed in how to use incident reporting systems.
b) Effective corrective and preventive actions are taken where necessary and improvements in practice are made.
GQ6 Risk assessments of the establishment's practices and processes are completed regularly, recorded and monitored
a) There are documented risk assessments for all practices and processes requiring compliance with the HT Act and the HTA's Codes of Practice.
b) Risk assessments are reviewed regularly.
c) Staff can access risk assessments and are made aware of risks during training.

Traceability standards
T1 A coding and records system facilitates the traceability of bodies and human tissue, ensuring a robust audit trail
a) There is an identification system which assigns a unique code to each donation and to each of the products associated with it.
b) A register of donated material, and the associated products where relevant, is maintained.
c) An audit trail is maintained, which includes details of: when and where the bodies or tissue were acquired and received; the consent obtained; all sample storage locations; the uses to which any material was put; when and where the material was transferred, and to whom.
d) A system is in place to ensure that traceability of relevant material is maintained during transport.
e) Records of transportation and delivery are kept.
f) Records of any agreements with courier or transport companies are kept.
g) Records of any agreements with recipients of relevant material are kept.

T2 Bodies and human tissue are disposed of in an appropriate manner
a) Disposal is carried out in accordance with the HTA's Codes of Practice. b) The date, reason for disposal and the method used are documented.

Premises, facilities and equipment standards
PFE1 The premises are secure and fit for purpose
a) An assessment of the premises has been carried out to ensure that they are appropriate for the purpose. b) Arrangements are in place to ensure that the premises are secure and confidentiality is maintained. c) There are documented cleaning and decontamination procedures.
PFE2 There are appropriate facilities for the storage of bodies and human tissue
a) There is sufficient storage capacity. b) Where relevant, storage arrangements ensure the dignity of the deceased. c) Storage conditions are monitored, recorded and acted on when required. d) There are documented contingency plans in place in case of failure in storage area.
PFE3 Equipment is appropriate for use, maintained, validated and where appropriate monitored
a) Equipment is subject to recommended calibration, validation, maintenance, monitoring, and records are kept. b) Users have access to instructions for equipment and are aware of how to report an equipment problem. c) Staff are provided with suitable personal protective equipment.

Appendix 2: Classification of the level of shortfall

Where the HTA determines that a licensing standard is not met, the improvements required will be stated and the level of the shortfall will be classified as 'Critical', 'Major' or 'Minor'. Where the HTA is not presented with evidence that an establishment meets the requirements of an expected standard, it works on the premise that a lack of evidence indicates a shortfall.

The action an establishment will be required to make following the identification of a shortfall is based on the HTA's assessment of risk of harm and/or a breach of the HT Act or associated Directions.

1. **Critical shortfall:**

   A shortfall which poses a significant risk to human safety and/or dignity or is a breach of the Human Tissue Act 2004 (HT Act) or associated Directions

   or

   A combination of several major shortfalls, none of which is critical on its own, but which together could constitute a critical shortfall and should be explained and reported as such.

   A critical shortfall may result in one or more of the following:

   (1) A notice of proposal being issued to revoke the licence

   (2) Some or all of the licensable activity at the establishment ceasing with immediate effect until a corrective action plan is developed, agreed by the HTA and implemented.

   (3) A notice of suspension of licensable activities

   (4) Additional conditions being proposed

   (5) Directions being issued requiring specific action to be taken straightaway

2. **Major shortfall:**

   A non-critical shortfall that:

   - poses a risk to human safety and/or dignity, or
   - indicates a failure to carry out satisfactory procedures, or
   - indicates a breach of the relevant CoPs, the HT Act and other relevant professional and statutory guidelines, or
   - has the potential to become a critical shortfall unless addressed

   or

   A combination of several minor shortfalls, none of which is major on its own, but which, together, could constitute a major shortfall and should be explained and reported as such.

   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, but which indicates a departure from expected standards.

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 or site visit.

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

Follow up actions

A template corrective and preventative action plan will be sent as a separate Word document with both the draft and final inspection report. You must complete this template and return it to the HTA within 14 days of the issue of the final report.

Based on the level of the shortfall, the HTA will consider the most suitable type of follow-up of the completion of the corrective and preventative action plan. This may include a combination of

- a follow-up site-visit inspection
- a request for information that shows completion of actions
- monitoring of the action plan completion
- follow up at next desk-based or site-visit inspection.

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