Site visit inspection report on compliance with HTA licensing standards

UK Biobank

HTA licensing number 12002

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**

21 and 26 September 2017

Summary of inspection findings

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

UK Biobank (the establishment) was found to have met all HTA standards.

The HTA has given the DI advice with regards to some aspects of governance and quality systems.

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

This report refers to activities carried out at UK Biobank (the establishment). The establishment is licensed for the storage of relevant material that has come from a human body for use in a scheduled purpose, under the Human Tissue Act 2004 (HT Act). Human samples are stored for use for the scheduled purpose of 'research in connection with disorders, or functioning, of the human body'.

The establishment has been licensed since 2007 and this was the second routine site-visit inspection to assess whether it continues to meet the HTA's standards. All standards were met in the previous inspection carried out in October 2010.

The establishment includes licensed premises in Cheadle (Greater Manchester), the hub site, and two satellite premises, located in Newcastle upon Tyne and Reading. The most recently licensed premises, in Reading, does not yet store relevant material and does not feature in this inspection report. There are overarching governance documents across all sites and there is a Person Designated (PD) appointed at each of the sites (see *Advice*, items 1, 2 and 4).

The establishment has two, ethically approved research tissue banks (RTBs) – UK Biobank (16/NW/0274) and Bloodwise (CellBank) (16/SW/0219). All samples held under the licence have been obtained from living donors. Since 2005, UK Biobank has recruited 500,000 participants in a prospective cohort study to determine causative effects in common, complex diseases. Samples of relevant material obtained, processed and stored include whole blood, saliva and urine. Samples were originally obtained at multiple collection sites across the UK and were transported for processing and storage at the hub site in Cheadle. Approximately 10 million samples from the original study are currently stored in a large (-80°C) robotic storage module. UK Biobank are inviting 100,000 participants back for further study. All baseline measurements are being taken again including samples of whole blood, urine and saliva. Samples are being obtained at three collection sites in the UK, including the Cheadle site, the Newcastle site and (from 2018) the Reading site. Samples are obtained and processed (aliquotted) on-site before being stored temporarily at -80°C at each satellite site. Once each month, samples are transferred from temporary storage to the hub site and into the large storage module in validated transport containers.

UK Biobank (Cheadle site) also stores bone marrow, cells, whole blood and cerebrospinal fluid in the Bloodwise (CellBank childhood leukaemia) RTB. There are approximately 90,000 samples stored in a -80°C freezer and in a liquid nitrogen storage tank.

All freezer areas are secured in designated laboratory areas with swipe card access. All storage facilities (storage module, reagent and contingency freezers and liquid nitrogen tanks) are fitted with automated alarms that are triggered by deviations from the set

acceptable temperature ranges. Members of the Operations team are immediately alerted by email when alarms are triggered. The alarm system is routinely tested every three months. All freezers have a CO_2 backup mechanism and the systems can maintain the correct temperatures for at least three days following a failure. The liquid nitrogen storage tank is in a secure area fitted with an oxygen monitoring system. There is no lone working. As well as back-up, the establishment has contingency arrangements for all temperature-controlled storage.

For the UK Biobank samples for further study, patients are contacted and sent relevant documentation including an information sheet and booklet. Once the participant agrees to take part in further study, consent is sought at the collection site using a computer-based questionnaire. Trained healthcare assistants are available to answer any questions the participant may have. Each participant is given a 12-digit unique patient identification number and all samples are labelled with a barcode, linking the sample to the unique ID. Once processed and aliquotted, each sample has a unique 2D barcode and is stored in a barcoded rack. The large freezer unit is robotically controlled and is connected to a remote computer system that can scan and log the racks and individual samples. The establishment uses an electronic Laboratory Information Management System (LIMS) to provide traceability of samples.

For the Bloodwise study, samples are initially quarantined from storage after receipt, being held only temporarily as back up for clinical purposes. There are 40 centres recruiting in the UK. Consent for the storage of these samples for research is required to be taken within 28 days; otherwise, samples are not stored and are disposed of. Consent is taken in a clinical setting and not by UK Biobank. Consent forms are available in multiple formats for a range of ages. Most of the samples held in the Bloodwise bank are from children and consent is obtained from the parents (see *Advice,* item 3). For Bloodwise samples, the child's initials and date of birth are used as the unique identification linked to all individual barcoded sample aliquots. All Bloodwise samples are stored in designated -80°C freezers and in a liquid nitrogen tank. Maintenance of the temperature-controlled storage is the same as with the UK Biobank samples, and traceability is maintained by the LIMS.

UK Biobank is an 'open access' resource and there is a rigorous application process before samples are approved to be sent out for research. The approval process includes registration to the resource, a preliminary application, a main application and material transfer agreements. Recommendations on each application are made by the UK Biobank Principal Investigator (or their designate) and are subject to confirmation by UK Biobank's Access Sub-Committee, a sub-committee of the UK Biobank board, comprising three professionals with scientific expertise. Records for this process are maintained and up to date for all samples.

Description of inspection activities undertaken

The inspection timetable was developed in consideration of the activities conducted under the licence, compliance update information, discussions with the DI, communications with the HTA and the findings of the previous inspection. The inspection included review of the establishment's procedures for conducting activities under the licence and interviews with the Operations Manager, Laboratory Manager, Quality Control Manager, Site Lead and two Phlebotomists who are involved in seeking consent. The inspection also included a visual inspection of the areas where samples are stored under the licence and audits of sample traceability. Audits of the following randomly selected samples were conducted:

- Ten samples, from consent to donation documentation to sample storage, from the UK Biobank site in Cheadle.
- Seven samples, from consent to sample storage, from the Bloodwise RTB in Cheadle.
- Ten samples, from consent to storage, from the UK Biobank site in Newcastle.
- Six samples, from storage to consent, from the UK Biobank site in Cheadle.
- Five samples, from storage to consent, from the Bloodwise RTB in Cheadle.
- Five samples, from storage to consent, from the UK Biobank site in Newcastle.

All samples were fully traceable for the UK Biobank study, at both sites, with no discrepancies noted.

UK Biobank are not responsible for obtaining consent for the Bloodwise study. In an audit of this RTB, all samples were traceable, from storage to consent to donation documentation and from consent to storage; however, two consent forms were incomplete and one consent form was filled out incorrectly (see *Advice*, item 3).

Inspection findings

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

Compliance with HTA standards

All applicable HTA standards have been assessed as fully met.

Advice

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

No.	Standard	Advice
1.	GQ1(d)	The DI is advised to consider having a standing agenda item for HTA matters. Minutes of governance meetings should be documented, including timelines for identified actions, and followed up. Minutes should be circulated to all relevant staff to help to ensure that they are aware of all important information relating to activities conducted under the HTA licence.
2.	GQ1(d)	The DI has nominated Persons Designated (PDs), who undertake key activities under the licence. The DI is advised to meet with all PDs named on the licence to strengthen the oversight of the licensed activity across the hub and satellite sites.
3.	GQ2(a)	Although appropriate consent had been given, for the Bloodwise RTB two consent forms were incomplete with the child's name missing and one had ticks in the check boxes instead of being initialled as per instructions. Although UK Biobank is not responsible for obtaining consent, it has responsibility to ensure valid and appropriate consent has been obtained for the samples it has received. The DI is advised to ensure that the audit schedule includes vertical audits of records and samples, from sample through to consent documentation. Records should be audited regularly to ensure completeness, accuracy and legibility.
4.	GQ5(a)	While non-conformance and incident procedures are documented and defined, the DI is advised to consider adding an appendix to the SOP to provide examples of what should be reported, including but not limited to; • specimen loss; • receiving and/or storing specimens without appropriate consent; • abnormalities in storage temperature readings; • inappropriate disposal; • storing or using human tissue after consent withdrawal; • sample mix-up.
5.	GQ5(b)	All non-conformances are recorded on a central spreadsheet; however, they are not easily identifiable by site. The DI is advised to break down the recorded non-conformances by site (include a site column) in order to monitor trends over the hub and two satellites.

Concluding comments

This report outlines the second, routine HTA site visit inspection of UK Biobank. A number of strengths and areas of good practice were observed during the inspection, including:

- The establishment has developed a robust system for sample traceability, including thorough practices for when samples are transported from the satellite site to the hub site. A fully automated system controls movement of all samples at the hub, ensuring a streamlined and accurate process.

- The establishment has developed a robust system for document management. An electronic document control system has been implemented to strengthen document control practices.

- The teams of staff that undertake key activities under the licence appeared very committed. The DI and team leaders meet regularly and demonstrated a willingness to work together to ensure compliance with the HTA's licensing standards. There appeared to be very good communication between staff.

- Staff at the establishment demonstrated that they strive towards improvement of practices, and were open to the advice offered by the HTA during the inspection.

- Staff training appears to be of a high standard. All staff working under the licence undergo MRC training to gain knowledge and awareness of human tissue legislation. Staff involved in obtaining patient samples undergo consent training and the DI performs regulatory training. Staff competency is assessed to three levels, and higher-level staff can train lower-level staff.

The HTA has assessed the establishment as suitable to be licensed for the activities specified.

Report sent to DI for factual accuracy: 24 October 2017

Report returned from DI: 2 November 2017

Final report issued: 13 November 2017

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.