

Site visit inspection report on compliance with HTA minimum standards

John Radcliffe Hospital

HTA licensing number 11106

Licensed for the

- **procurement, processing, testing, storage, distribution and import/export of human tissues and cells for human application under the Human Tissue (Quality and Safety for Human Application) Regulations 2007; and**
- **storage of relevant material which has come from a human body for use for a scheduled purpose**

17-18 January 2017

Summary of inspection findings

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

John Radcliffe Hospital (the establishment) was found to have met all HTA standards.

The HTA undertook this inspection as a joint inspection with the Human Fertilisation and Embryology Authority (HFEA). The HTA regulates the procurement, donor testing, processing, storage, distribution and import of tissues and cells including reproductive tissue intended for human application *i.e.* transplantation. The HFEA regulates fertility treatment, and storage of ovarian or testicular tissue intended for *in-vitro* maturation of gametes. Both regulators assess compliance with standards in accordance with the European Union Tissues and Cells Directives (Directives 2004/23/EC, 2006/17/EC, 2006/86/EC, 2012/39/EU).

This inspection report covers the assessment of the HTA licensing standards; a separate report with covers the assessment of HFEA licensing standards will be issued by the HFEA.

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

The HTA's regulatory requirements

The HTA must assure itself that the Designated Individual, Licence Holder, premises and practices are suitable.

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.

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.

Licensable activities carried out by the establishment

'E' = Establishment is licensed to carry out this activity.

'E*' = Establishment is licensed to carry out this activity but is not currently carrying it out.

'TPA' = Third party agreement; the establishment is licensed for this activity but another establishment (unlicensed) carries out the activity on their behalf.

Tissue type	Procurement	Processing	Testing	Storage	Distribution	Import	Export
Heart valves, patches and conduits	E/TPA	E	SLA	E	E/TPA		E*
Ovarian and testicular tissue	E/TPA	E	SLA	E	E	E	E*
Ocular tissue	E						

Background to the establishment and description of inspection activities undertaken

The Oxford Cell and Tissue Biobank (OCTB) formerly known as the Oxford Heart Valve Bank was set up in 1991 and has held a licence from the HTA since 2007.

The Oxford University Hospitals NHS Foundation Trust is the corporate licence holder. The HTA Designated Individual (DI) is the Director of OCTB. The corporate licence holder contact is a Paediatric Oncology Consultant and Lead Consultant for the Gonadal Tissue Cryopreservation Programme. Operational staff include the Director, two tissue coordinators, three processing technicians and a quality manager. Clinicians based at the Department of Obstetrics and Gynaecology, Women's and Children's Hospital and the Oxford Fertility Unit provide training and advice as required.

The OCTB is located at the Heart Centre at John Radcliffe Hospital, Oxford, and consists of a clean room suite and an office area. Cardiac and reproductive tissues are stored in four liquid nitrogen storage vessels in a portacabin located in the immediate vicinity of the Heart Centre. Staff enter the portacabin using a key which is kept in the OCTB. Security arrangements include regular patrols in the area; there is no intruder alarm and continuous CCTV monitoring does not take place (see advice item 3).

The establishment has an agreement with a clean room monitoring and validation service which covers monitoring of the clean room suite, sampling of viable and non-viable particulates (active air sampling, contact and settle plates, swab tests) and provision of a monthly report to the OCTB. The Microbiology Department at John Radcliffe Hospital undertakes product testing and microbial testing of transport fluid and washings of tissues.

Donor blood samples are centrifuged, frozen and stored at -80°C . The samples are sent to another HTA-licensed establishment for serology testing and nucleic acid testing under a service level agreement.

The temperature of the liquid nitrogen storage vessels and the -80°C freezer is monitored using a proprietary temperature monitoring system with an automatic call-out system. Staff are on-call 24 hours a day and respond whenever an alarm is triggered.

The fifth routine inspection of the OCTB was undertaken on 17 and 18 January 2017. Day one focused on activities relating to reproductive tissues and was jointly undertaken with the HFEA. Day two covered cardiac tissues stored under the HTA licence. The inspection included a visual inspection of the premises where tissues are processed and stored, individual and group discussions with key members of staff and a review of documents and clinical notes. This inspection did not cover tissues stored for the scheduled purpose of research.

During the joint inspection HFEA inspectors reviewed the consent process, which covered storage of tissues and oocytes as appropriate. Parental consent is sought if the donor is below 18 years of age and not competent to give consent. Donors are re-consented when they reach 18 years of age.

Since the previous inspection, the ONE Study trial (EudraCT 2013-002099-42) at OCTB completed recruitment of donors and ceased collecting whole blood by venesection.

Trained OCTB staff seek consent, undertake donor assessment and retrieve eyes from deceased donors. The eyes along with a sample of blood are sent to another HTA-licensed tissue bank for processing and storage for human application.

Heart valves, patches, conduits and ocular tissue

OCTB Tissue coordinators attend the mortuary each morning where they are made aware of any recent deaths. They contact Bereavement services, check the organ donor registry and review patient medical files in order to determine if the deceased could potentially be an eye and/or heart valve donor. The tissue coordinators contact the nearest relatives to discuss the possibility of donation. Once sufficient time has elapsed for the request to be considered and if the relatives agree, they seek formal consent and collect information about the donor's social and behavioural history. Consent is also sought for taking a blood sample from the deceased, if a pre-mortem sample is not available for testing in the Biochemistry laboratory. The deceased person's GP is contacted for further information. The tissue coordinators record consent conversations for audit and training purposes.

The OCTB processes heart valves and patches from whole hearts retrieved at the John Radcliffe Hospital and from other hospitals in the region. Trained OCTB staff retrieve hearts at the John Radcliffe Hospital and retrieval surgeons who work in National Organ Retrieval service teams retrieve hearts from hospitals in the region. Hearts are dissected and aortic and pulmonary heart valves, and tissues such as cardiac patches and conduits used for reconstruction and repair, are processed in the clean room suite. Cardiac tissue is packaged in cryopreservation medium, cryopreserved and stored in the vapour phase of liquid nitrogen. The OCTB keeps records of heart valves, conduits and patches, which are ready to be issued for clinical use. These records are sent to the National Fulfilment Service which is a national database administered by NHS Blood and Transplant. The National Fulfilment service allocates cardiac tissue to end users throughout the UK.

Couriers who work under a third party agreement with the establishment distribute cardiac tissue. Tissue is packed in a dry shipper or in dry ice. If the tissue is not used, the DI can authorise the return of unopened dry shippers or other transport boxes from the end user, back to the OCTB. Returned tissue is placed in a dedicated section of a -80°C freezer for up to six months and is only released to the surgical centre which originally requested the tissue.

The establishment recently changed one of the components of the antibiotic cocktail used to decontaminate cardiac tissue before it is cryopreserved. The establishment commissioned the same organisation which undertakes environmental monitoring of the clean room facility, to assess the potency and effectiveness of the new cocktail; the validation was shared with the HTA.

Reproductive tissue

Since 2013, the OCTB has been storing reproductive tissue for autologous use. The OCTB has procured reproductive tissue from over 120 donors and set up a support service to fund donation and storage. Reproductive tissue is obtained from women and children before they undergo radiotherapy or chemotherapy treatment for cancer, as they are likely to be sub-fertile or infertile following such treatment. In 2016, the OCTB began storing testicular tissue from pre-pubescent boys, following HTA authorisation of a preparation process dossier for processing of testicular tissue.

Oncology centres at the John Radcliffe Hospital and other hospitals provide information about fertility preservation to potential donors. Clinicians refer potential donors to the OCTB and a senior clinician at the OCTB seeks consent in accordance with HTA and HFEA requirements. The establishment has a system in place to re-consent donors who are children, once they reach 18 years of age. The OCTB arranges with the referring centre to retrieve ovarian or testicular tissue within seven days of referral. OCTB staff are always present in theatres during procurement. The OCTB provides training and standard operating procedures to staff

at other centres who procure tissue under third party agreements. The agreements cover the role and responsibilities of OCTB staff and staff at the procuring establishment, and the provision of theatres and sterile equipment. OCTB staff bring retrieval kits with them and are always present in theatres during the World Health Organisation (WHO) surgical safety checklist sign-in, and time-out procedures. Following procurement, OCTB staff transport the tissue back to the OCTB for processing in the clean room suite.

Ovaries are dissected, the medulla removed and the ovarian cortex is sliced and placed in cryopreservation media. Until recently, oocytes present in the medium surrounding the cortical slices were aspirated and sent to a nearby fertility clinic licensed by the HFEA. The quality control steps include testing the transport fluid and the final suspension in cryopreservation fluid for microbial contamination and histological evaluation of the ovarian tissue to detect malignant cells. Histological evaluation along with immunohistochemical staining and molecular studies to detect tumour-specific markers will be repeated before ovarian tissue is returned to and implanted into the donor. The HTA team was informed that if any of the donors tested positive for mandatory disease markers, tissues would be stored in a separate quarantine tank.

Document review

Standard Operating Procedures (SOPs), policies, minutes of meetings, audit schedules, induction and training records, competency assessments, cleaning records, results of operator specific broth transfer and hatch transfer competency assessments were reviewed. Audit trails relating to cardiac tissues, ovarian, and testicular tissues were reviewed. Records relating to consent, procurement, donor serological test results, processing, sterility testing (transport fluid, cryomedium), consumables used during processing, cryopreservation, environmental monitoring, pressure cascades, histology, and sign-off by senior members of staff were reviewed as appropriate to the case being reviewed. There were no discrepancies (see advice item 1). HFEA inspectors reviewed the consent procedure relating to ovarian tissue and the system of audits, incident reporting and investigation.

Inspection findings

The HTA found the Designated Individual and the Licence Holder 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.	C1d, GQ1i, GQ4f, GQ5c,	Donor and processing data for each procurement of reproductive tissue is reviewed in accordance with the establishment's 'Quality Assurance review' procedure. The DI is advised to review donor and processing files to ensure all documentation including test results and donor information are filed and checked soon after processing. This would help to ensure that any quality issues or deviations are identified soon after processing and addressed in a

		timely manner. These tissues may be stored for several decades and delays in sign-off could make it difficult for legacy records to be retrieved as software systems and records may become inaccessible.
2.	GQ2b	The DI is advised to consider implementing a system of observational audits for processing of reproductive tissue. Two members of staff work at adjacent Class II cabinets within the clean room to process and cryopreserve reproductive tissue from each donor. Whilst they witness each other at key stages, they do not observe all of the steps carried out by the other person.
3.	GQ5d	Donor test results are transcribed from laboratory reports onto a form which lists all tests. The phrase 'not detected' is pre-printed in the results section relating to each test. Staff amend this pre-printed result if the test is positive and change it to read 'detected'. The DI is advised to either, remove the pre-printed phrase- 'not detected' or replace it with - detected/not detected - when the form is next updated. This will ensure that staff have to modify the results box whenever they record a test result, making it easier to check if a test has been recorded.
4.	GQ7a	The OCTB currently reports incidents relating to whole hearts retrieved by NORS teams via the NHSBT incident reporting system relating to organ donation and transplantation. The DI is advised to additionally report potential serious adverse events and reactions to the HTA through the Human Application incident reporting portal as these incidents could also impact on the quality and safety of any cardiac tissue that has been processed.
5.	PFE1	During the inspection, the DI was advised to strengthen the security of the portacabin where autologous reproductive tissue and heart valves are stored. The DI informed the HTA that security staff have agreed to change their procedures; they will physically check the door of the portacabin when they undertake routine patrols in the area. The HTA understands that there are plans to relocate the liquid nitrogen storage vessels from the portacabin to the ground floor of the Women's and Children's Hospital. The DI is advised to bring these plans forward as this will improve security of the tissues in storage. The DI is advised to undertake a risk assessment of this change, as part of the change control procedure.

Concluding comments

The OCTB has an effective system of governance. There is good communication between staff and management. The OCTB is supported by senior managers within the Trust, and Board members include medical, surgical, microbiology and fertility advisors. Procurement of reproductive tissues is regarded as an emergency procedure and operating theatres are made available as needed.

OCTB staff are always present in theatre when reproductive tissue is procured. Consent forms for autologous donation of reproductive tissue includes a statement, by the consent seeker, which states that he/she considered whether or not the donor required a translator. Staff inoculate broths with the test fluid in the clean room so as to minimise contamination which may occur if the broths are inoculated in the microbiology laboratory. A detailed checklist is placed in each processing file to ensure that all documentation has been filed.

Staff demonstrated a strong commitment to improvement and developing new procedures.

The HTA has given advice to the Designated Individual with respect to the quality review procedure and observational audits for reproductive tissue, updating forms used to record test results within the donor file, reporting adverse incidents to the HTA and strengthen security of the storage facility.

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

Report sent to DI for factual accuracy: 21 February 2017

Report returned from DI: 11 April 2017

Final report issued: 13 April 2017