Sheffield Teaching Hospitals NHS
NHS Foundation Trust

Research Department

STANDARD OPERATING PROCEDURE

The Use of Human Tissue in Research

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Approved by (name & role)	Dipak Patel Research Manager	**Date:** 12 Feb 2019	**Signature:**

Standard Operating Procedure: Research Department

The Use of Human Tissue in Research

This SOP has been produced in accordance with the Human Tissue Act 2004 and the Codes of Practice issued by the Human Tissue Authority. It outlines the current procedures to be followed when Investigators intend to use human material in research.

Background

The Human Tissue Act 2004 received Royal Assent on 15 November 2004 and was fully implemented on 1st September 2006. The purpose of the Act, which is not retrospective, is to provide a consistent legislative framework for issues relating to body donation and the removal, transfer, storage and use of human organs and tissue. It makes consent the fundamental principle underpinning the lawful storage and use of human bodies, body parts, organs and tissue and the removal of material from the bodies of deceased persons.

The Human Tissue Authority (HTA) was established in April 2005. The HTA has issued Codes of Practice and is the Authority which regulates the use of human tissue for the 'Scheduled Purposes' covered by the Human Tissue Act, one of which is research. The HTA grants licences to establishments in order that they can carry out certain activities lawfully, such as the storage of tissue for research. The University of Sheffield currently holds a HTA licence for the storage of tissue for research purposes (HTA Licence Number 12181). Further information on licensing can be found on the HTA website.

Investigators using human tissue for research must adhere to the HTA Codes of Practice, and any updates released.

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1. Acronyms

DNA	Deoxyribonucleic Acid
CRIO	Clinical Research & Innovation Office
FAQs	Frequently Asked Questions
HTA	Human Tissue Authority
HRA	Health Research Authority
IRAS	Integrated Research Application System
RMS	Research Management System (RMS)
RNA	Ribonucleic Acid
REC	Research Ethics Committee
SOP	Standard Operating Procedure
STH	Sheffield Teaching Hospitals NHS Foundation Trust
TUoS	The University of Sheffield

2. Definition of Relevant Material

Relevant material covered by the Human Tissue Act is defined as human tissue that has come from a human body and consists of, or includes, human cells. Blood, urine, teeth, sputum from the living are all relevant materials. Hair and nails are relevant from the deceased but not the living.

Embryos and Gametes are excluded from the Human Tissue Act, as they are covered under the Human Fertilisation and Embryology Act.

Tissue that is not relevant includes acellular plasma and serum, DNA and RNA.

2.1 Categories of relevant material

2.1.1 Specifically identified relevant material: includes bodily organs and tissues, consisting largely or entirely of cells, and clearly identifiable and regarded as such. This category of relevant material includes human bodies, internal organs and tissues, skin, teeth and bone.

2.1.2 Processed material: includes plasma or serum. Where material has been processed to render acellular, this is not regarded as relevant material. The HTA may require assurance that the process in question had been carried out. Under this category plastinated tissue and plastinated body parts (where the cellular structure is retained by the plastination process) are to be regarded generically as relevant material.

2.1.3 Bodily waste products (including excretions and secretions): is a less well characterised group of material. The HTA considers bodily waste should normally be regarded as relevant material. There will be cases where a researcher believes that material, intended for a scheduled purpose, is actually acellular. In such cases the researcher would need to consult the HTA, and we would then refer the case for advice to a members' panel if necessary.

2.1.4 Cell deposits and tissue sections on microscope slides: In general cell deposits or tissue sections on microscope slides are considered relevant material. This is because such deposits or sections are likely to contain whole cells or are intended to be representative of whole cells.

Also see the HTA website for an up-to-date List of materials considered to be 'relevant material' under the Human Tissue Act 2004

2.1.5 Cell Lines: Cell lines which have divided in cell cultures or have been purchased from suppliers are not licensable and are not considered “relevant material” under the Human Tissue Act. Primary cells however are relevant material and licensable under the Human Tissue Act.

3. Procedure to be followed by Investigators prior to, during and after a research project has ended

3.1 Prior to Research Project Commencing

Investigators will refer to the Clinical Research & Innovation Office (CRIO) website http://www.sheffieldclinicalresearch.org/ for advice on the use of human tissue in research and will familiarise themselves with the content of the Human Tissue Act and the Codes of Practice issued by the HTA and Health Research Authority (HRA) guidelines.

All research staff involved in studies where tissue is collected, used and/or stored should be aware of the HTA Codes of Practice; A-‘Guiding Principles and the Fundamental Principle of Consent’, and E- ‘Research’ which are available on the HTA website.

The CRIO also recommends that all staff involved in human tissue research studies and especially those taking consent should complete HTA training.

3.1.1 HTA training

There are currently two options for online training:

- MRC e-learning: Research and Human Tissue legislation, this comprises 7 modules and an assessment with 10 questions and a pass mark of 70%

- HRA research involving human tissue, this comprises 5 modules and a knowledge test with 10 questions and a pass mark of 80%. NB: The HRA online training is not compatible with internet explorer

All training should be recorded locally (such as on the study delegation log or held centrally with training records) and should be renewed every **two** years.

GCP training is also recommended for all staff taking consent.

3.1.2 Protocols

Investigators will ensure that the study protocol covers the following:

a) the source of tissue samples to be used in research
b) the consent procedures for use of donated tissue samples in research
c) the anonymisation arrangements for tissue samples if they are to be anonymised
d) the transfer and storage arrangements for tissue samples both during the project and after the project ends
e) the arrangements for the recording / traceability of the collection and use of tissue samples

The Investigator must ensure that the project has the appropriate Research Ethics Committee approval and has been authorised by the CRIO prior to commencing the research.

3.2 During the conduct of the Research Project

3.2.1. Consent: Investigators intending to use samples taken specifically for research, must always obtain informed consent from the donor for this use. The signed informed consent forms must be kept in both the investigator site file and in the medical notes of the patient.

The only exceptions to obtaining consent are if:

- the tissue was collected before 1 September 2006
- the tissue has been taken from a living person and the researcher is not able to identify the donor and the research is ethically approved by a Research Ethics Committee
- it is imported tissue.

Appropriate consent is always required under the Human Tissue Act to remove tissue from the deceased for research purposes.

Under the Codes of Practice issued by the HTA, anonymised samples need not be 'permanently and irrevocably unlinked'. Although the researcher using the material **must not** hold any information that identifies a donor, links can be retained to the donor of the tissue sample by an intermediary person or organisation acting to protect the identity of the donor.

The HTA Codes of Practice also state that, in certain circumstances, Ethics Committees can stipulate irrevocable unlinking and may also stipulate that consent ***is*** required.

Where investigators are required to obtain a donor's consent, investigators must ensure that Participant Information Sheets state clearly the intention to use tissue samples taken at clinic or surgery in research. The Participant Information Sheet should contain sufficient information so that it is clear to the participant, within the description of study procedures, the nature of the tissue sample to be donated and state:

- whether new tissue samples will be taken as part of the research (e.g. blood, tissue, specifically for this study)
- whether tissue samples excess to a clinical procedure will be asked for
- access to existing stored samples will be asked for
- the security procedures in place for collecting, using and storing samples
- whether there will be any possible intended use in the future for research that cannot yet be specified (A separated or two part consent form is recommended if future use is intended, and it should be clear if further ethical approval will be sought)
- whether tissue samples will be used for genetic testing
- who will have access to use the tissue sample
- the level of confidentiality (for this study and for storage for future studies)
- provision for destruction of the tissue sample after use in research
- procedures for possible feedback of individually significant information from their use
- whether tissue samples will be transferred outside the UK

There must be a section on the Consent Form which allows for the recording of a donor's explicit consent for the use of their tissue, and consent for future use.
Investigators taking consent should record the process in the patient's notes and file a copy of the Participant Information Sheet and signed Consent Form in the patient notes. The original signed Consent Form should be kept in the study site file.

Where an investigator wants to obtain tissue samples from children, the consent process must include assent from the child (if applicable age) and consent from the parent or legal guardian if under 16 years of age.

Where an investigator cannot obtain consent from a donor due to the disability/incapacity of that individual, the consent process must be witnessed by another party independent of the research team. The Human Tissue Act details those individuals with 'qualifying relationships' allowing those individuals to give consent on behalf of the incapacitated donor.

Where an investigator wishes to use tissue samples from the deceased, consent is always required unless the tissue samples were obtained before 1 September 2006. A person may consent for their tissue to be used for research after their death. If there is no record of the deceased wishes, consent can be obtained from relatives or a person acting on the deceased's behalf.

Relevant material held in diagnostic archives does not need to be stored under the HTA licence, providing all the samples are for diagnosis. Tissue samples can be accessed by investigators with appropriate ethical approval, see External Tissue sample requests SOP B134.

3.2.2 Storage: Investigators must ensure all tissue samples taken and kept in storage for the purposes of a research project are appropriately labelled upon collection of the sample.

Investigators must keep a record of the tissue samples they receive during the conduct of a research project in order that the origin, storage location, use and final destination of tissue samples collected as part of the research can be traced. A copy of a tissue sample collection record and tissue sample tracking form must be kept by the investigator. See Appendix 1 and Appendix 2 of this SOP for a sample tissue collection record and tissue sample tracking form. Traceability of tissue samples is a requirement of the Human Tissue Act.

During an active Research Project, tissue must be stored as described in the approved Ethics application, or in a HTA licensed tissue bank if a Research Project has Ended

3.3 Following the end of the Research Project

The end of a study is defined as the date recorded on the IRAS application form. For studies requiring extension, the Investigator should inform the CRIO one month prior to the end date. The allocated Research Coordinator will support the study team in completing the relevant forms / HRA procedures and collating the necessary study documentation.

Following the study end date the tissue is no longer under regulatory approvals. The Investigator should complete an End of Study REC Report and send it to the REC and copy in the CRIO. In exceptional circumstances when a study has gone past its REC end date without an extension, the Investigator is required to contact the HTA Lead in the CRIO for advice and support.

The Investigator must ensure that any tissue samples remaining following the end of the study are either disposed according to local STH and University of Sheffield policies (whichever applies to the site where the research is undertaken) and in accordance with Research Ethics Committee approval for the study and the HTA Code of Practice. If the investigator wishes to keep the relevant material samples they must be transferred into a premise which holds a HTA Research License.

Investigators who wish to retain remaining 'relevant material' samples following the closure of a research project must ensure that the samples are stored in a premise which holds an HTA Research License, such as the Sheffield Biorepository. Once samples are stored within a HTA Licenced facility, they can be adopted into the Research Tissue Bank (with agreement of the CI) or can be held in the facility and only accessed for use, once a subsequent research project obtains REC approval, and relevant NHS permissions.

For details of the procedure to be followed when intending to transfer tissue into the Biorepository contact Biorepository@sheffield.ac.uk or Jemima.Clarke@sth.nhs.uk at the CRIO.

3.3.1 HTA Ended Studies Exercise

To ensure STH compliance with the above mentioned “End of Study” requirements for tissue samples, the CRIO performs the “HTA ended studies exercise” on a six monthly basis.

This is an audit of all studies recorded on the CRIO Research Management System (RMS) as:

- Tissue samples = Yes
- Project status = Ended
- End date = < or = to 6 months

The results of the above RMS query are extracted into an excel spreadsheet and the CRIO Coordinator sends an e-mail to PIs to check the status of tissue samples following the end of the study. The email template (see Appendix 3) is available on the CRIO Network drive.

The PI or nominated study team member then notifies the CRIO of the status of tissue samples, which is recorded in the RMS Diary Page. If any issues are raised by this exercise, the CRIO Coordinator, with the assistance of the HTA Lead will follow up the matter until a suitable outcome is attained.

4. DNA Analysis and Research

DNA (as opposed to the bodily material from which it originates) is not considered to be relevant material under the Human Tissue Act. In all but exceptional cases (such as the prevention or detection of crime), the law requires that consent is obtained from the person whose DNA is to be tested.

According to the HTA Codes of Practice on Research: The results of DNA analysis can be used for research without consent, providing the bodily material from which the DNA is extracted:

- is from a living person; and
- the researcher is not in possession, and not likely to come into possession of information that identifies the person from whom it has come; and
- the material is used for a specific research project with recognised ethical approval.

Although no offence will be committed in this situation, the HTA recommends that, where practical, consent is obtained. An offence will be committed where somebody has bodily material intending to analyse its DNA and use the results for research without consent for non-excepted purposes. For more information on excepted purposes, see the section on consent and use of DNA in the Code of Practice on Consent on the HTA website. The HTA website also has useful FAQs information for reference.

5. Ethical Approval of Research Tissue Banks

A ‘research tissue bank’ (or ‘Biobank’) is defined as: ‘A collection of human tissue or other biological material, which is stored for potential research use beyond the life of a specific project with ethical approval or for which ethical approval is pending.’

The HTA and HRA have agreed a position whereby NHS Research Ethics Committees (RECs) can give generic ethical approval for a research tissue bank's arrangements for collection, storage and release of tissue, providing the tissue in the bank is stored on HTA-licensed premises. This approval can extend to specific projects receiving non-identifiable tissue from the bank. The tissue does not then need to be stored on HTA-licensed premises; nor does it need project specific ethical approval.

The HRA has facilitated ethical review of research involving human tissue:

- A Research Ethics Committee approval process for HTA licensed tissue banks, allowing tissue to be released to research projects without further REC approval within the conditions agreed in the original ethical approval. See HRA website for details of the review process for research tissue banks.
- Where this “generic ethical approval” applies, storage of the tissue by the end user researcher will not need a HTA license. Once the research project is finished the researcher will need to transfer the tissue to a licensed tissue bank or, as a last resort, dispose of the material.
- The establishment of 'flagged' Research Ethics Committees which will specialise in tissue bank applications. Applications to undertake specific research projects involving tissue may continue to be submitted to any Research Ethics Committee.

To apply for ethical review either for a specific project or a tissue bank is via IRAS. Question-specific guidance is available for applicants on-line.

In addition to ethical approval, NHS Permission at each Tissue Collection Centre is required prior to the start of the Research.

For studies linked to a tissue bank, NHS Permission may be required for each sub-study and the Investigator should contact the CRIO for advice.

Annual progress reports will need to be submitted to the Research Ethics Committee. Any changes to the study documentation will need to be submitted to the Sponsor for classification. All substantial amendments will require ethical review.

Research Ethics Committee approval for a tissue bank is valid for five years. If at the end of the 5 years the Investigator wishes to renew the tissue bank they need to apply to the same Research Ethics Committee before the expiry date. The Investigator should inform the Sponsor two months in advance who will in turn support them with the application.

6. Import and Export of Tissue Guidelines

The following information is from current HTA guidance.

6.1 The import of tissue

The import of human tissue is not itself a licensable activity under the Human Tissue Act. However, once tissue is imported, its storage or use for a scheduled purpose (including research) is licensable unless the samples are for use in a specific research project which has a valid approval from an NHS Research Ethics Committee. Imported tissue should therefore be stored in a HTA licensed tissue bank unless they are being held for a specific ethical approved project.

If an application to a Research Ethics Committee is required, the researcher should provide the committee with assurances that the tissue was obtained ethically and in accordance with the ethical and legal requirements of the donor country. Currently, HRA guidance to Research Ethics Committees is to confine ethical review to research activities conducted in the UK. Provided appropriate assurances are given, no further detailed review will be undertaken of the consent arrangements in the donor country.

6.2 The export of tissue

There is no legal requirement for obtaining ethical approval from a NHS Research Ethics Committee to export tissue samples overseas. NHS Research Ethics Committees will not scrutinise overseas research projects where the only involvement in the UK is to send tissue samples to overseas collaborators and instead ethical review will be confined to the activities

conducted in this country, for example the process of informed consent. It is good practice to inform tissue donors of the intention to transfer their samples overseas within the information sheet and consent form.

7. Material Transfer Agreements

Investigators who wish to involve STH in the transfer of human tissue from external organisation (including import/export) must ensure that such activity is only carried out under the terms of a Material Transfer Agreement. STH has developed a Material Transfer Agreement and SOP for this purpose (SOP C116).

Please contact the CRIO for further information on the use of Material Transfer Agreements in research.

8. HTA Contact Details

If you have any queries regarding the use of human tissue in research please contact the HTA lead Jemima.clarke@sth.nhs.uk.

The contact at the University of Sheffield Research Office is Lindsay Unwin, l.v.unwin@sheffield.ac.uk.

The email contact for the Biorepository is Biorepository@sheffield.ac.uk

Investigators based at Sheffield Hallam University should contact Dr Anita Gurney (a.gurney@shu.ac.uk) for details of SHU policy and guidance.

Appendix 1. Tissue Sample Collection Form

Study No:	
Study Title:	
Investigator name:	

Subject No	Subject consent (dd-mmm-yyyy)	Date sample collected (dd-mmm-yyyy)	Sample type	Storage location & type of facility[1]	Storage period		Final location[2]	Person Responsible
					Form	To		

[1] Please specify full address and type of storage facility

[2] Please specify name of recipient of tissue (e.g. academic collaborator or Commercial company) and location

Appendix 2. Tissue Sample Tracking Form

Study No:	
Study Title:	
Investigator name:	

Sample No	Date Sample Taken from storage for Analysis (dd-mmm-yyyy)	Sample storage location during analysis	Outcome of analysis	Sample returned to original storage location (freezer/fridge/ archive)	Final location of sample	Person Responsible	Additional Information

Appendix 3. HTA Ended Studies Exercise – email template

Sent on behalf of Professor Chris Newman, Designated Individual for the Human Tissue Authority (HTA) License for Storage of Tissue for Research and Professor Simon Heller, Director of R&D Sheffield Teaching Hospitals NHS FT

Dear Investigator

In accordance with the Human Tissue Act 2004, it is a ***legal*** *requirement* to ensure human tissue stored for research, once NHS Research Ethics Committee (REC) approval has ended, is either disposed of appropriately or transferred into a HTA licensed facility. The Sheffield Biorepository is the only facility within STH and the University of Sheffield's Medical & Dental Schools with a HTA license to hold tissue for research purposes (outside of a REC approved research project)

Our records show your study has ended and is listed as having had tissue samples:

STH ref: STH12345
Study Title: xxxx
Study end date: DD/MM/YYYY

Please reply to name.name@sth.nhs.uk by ***DD/MM/YYY***

Confirm which of the following statements is correct for the above study by putting an 'X' in the middle column against the relevant statement, providing the additional information where applicable:

	Request for information	'X'	Additional information
1.	Your study has ended and there is *no remaining tissue*		
2.	Your study has ended, there is *remaining tissue* and;		
	a) the tissue has been disposed of appropriately; OR		
	b) the tissue has been transferred to the Sheffield Biorepository or to an external CI for storage in an external HTA licensed tissue bank; OR		Transferred to:
	c) the tissue remains in your possession		Storage location: Type of tissue:
3.	Your study has not ended; please advise us of the correct end date for your study		Proposed end date:

Appendix 4. Associated Documents

	Document	Research Department Network Location	Website	Alfresco	Created by
1	Tissue sample collection form	T:\Research\General\Research Governance\Human Tissue Research\Useful documents\sample collection log V1.doc	Yes	Yes	GM
2	Tissue sample tracking form	T:\Research\General\Research Governance\Human Tissue Research\Useful documents\sample tracking form V1.doc	Yes	Yes	GM
3	HTA Ended Studies Exercise – email template	S:\General\Research Governance\Human Tissue Research\HTA Ended Study Declaration	No	Yes	NT
4	SOP for Material Transfer Agreement	T:\Research\General\Research Governance\SOPs\Current SOPs\new C series\C PDF\SOP C116 MTA V2 11SEP13.pdf	Yes	No	GM

Appendix 5. SOP revisions and history

SOP number & version	Effective date	Reason for change	Author
THIS SOP			
6.0	01 Mar 19	Updated to reflect change in HTA Licence Holder from STH to TUoS Updated staff changes and removed weblinks Added HTA Ended Studies process	JC
PREVIOUS SOPs			
3.0	23 Jul 13	Replaces SOPs A130 and B115	JB
4.0	01 Nov 14	Update contact details/terminology and transfer to new SOP template	NT
4.1	01 Apr 15	Clarification of end of study and addition of consent requirements.	NT, JC
5.0	01 Nov 17	Clarification on HTA training and diagnostic archives	NT