Standard Operating Procedure

RESEARCH STUDY SAMPLES

SETTING Trustwide for research conducted within UHBristol and/or sponsored by UHBristol

AUDIENCE Research and laboratory staff processing biological research samples for research conducted at UH Bristol

ISSUE Processing and handling of research study samples

QUERIES Research Operations Manager or Research Management Facilitators - Research & Innovation Department via 0117 342 0233

Document History

SOP number	SOP 013	**SOP Version**	1.3
Effective Date	21/FEB/2018	**Review Date**	21/FEB/2020

1. Introduction

Review date	Version number	Version date	Effective date	Author/ Reviewer	Authorised by
N/A	V1.0	14/SEP/15	03/NOV/15	Jessica Bisset	Diana Benton
02/DEC/2015	V1.1	02/DEC/15	23/DEC/2015	Jess Bisset	Diana Benton
November 2016	V1.2	28/NOV/16	23/DEC/2016	Jess Bisset	Diana Benton
January 2018	V1.3	16/JAN/18	21/FEB/2018	Jake Harley	Jess Bisset

Version Number	Reason for change
Original V1.0	n/a original document
V1.1	Minor updates and clarifications
V1.2	Minor updates and clarifications
V1.3	Minor updates and clarifications

1. Introduction

UH Bristol laboratory departments are accredited to comply with regulatory standards and hold a wealth of experience and expertise to support research. Laboratory medicine at UH Bristol covers Blood Sciences (Haematology and Clinical Biochemistry), Histopathology, Flow Cytometry and Aspiration. North Bristol NHS Trust provide Cellular Pathology services (under a service level agreement with UH Bristol) and host the Public Health England laboratories.

Any laboratory work carried out for the purposes of a research study must be done in accordance with the relevant study documentation (protocol, participant information sheet, consent form) and all applicable regulations including The Medicines for Human Use (Clinical Trials) Regulations 2004 (and any amendments) for Clinical Trials of Investigational Medicinal Products (CTIMPs).

2. Purpose

The purpose of this SOP is to describe the minimum standards required for the processing and handling and storage of biological research samples on UH Bristol NHS Foundation Trust managed premises, and/or at external laboratories contracted by UH Bristol to process research samples (as relevant).

3. Scope

In Scope: Mandatory for UH Bristol sponsored CTIMPs and externally sponsored CTIMPs where the minimum standards defined by the sponsor do not meet those described within this SOP or agreement to use a different SOP(s) has not been made by sponsor. Good practice for all other relevant research.
Out scope: Laboratory processes carried out within UHBristol for provision of clinical services. Laboratories hosted within UHBristol premises, but managed by other organisations (e.g. University of Bristol), except where otherwise defined within the SOP.

4. Responsibilities

All research staff handling and processing study samples are responsible for ensuring appropriate consent has been sought for those samples and that they are managed in accordance with the study protocol.
Laboratory staff are responsible for ensuring all research samples are processed in accordance with the protocol, laboratory manual (where available) and all applicable standards and regulations.

5. Abbreviations and Definitions

Abbreviations	
CI	Chief Investigator
CSV	Computer System Validation
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
PI	Principal Investigator
UH Bristol	University Hospitals Bristol NHS Foundation Trust

6. Procedure

6.1 Engagement with UH Bristol laboratory

- CI/PI and research teams must engage at an early stage in the development or setup of research requiring use of a laboratory to ensure proper input is gained. As mentioned Laboratory medicine at UH Bristol covers Blood Sciences (Haematology and Clinical Biochemistry), Histopathology, Flow Cytometry and Aspiration. Cellular Pathology services are provided by North Bristol NHS Trust for UH Bristol under a Service Level Agreement. Also hosted by North Bristol NHS Trust are the PHE laboratories, these labs are also subject to this SOP. Contact details can be provided by the R&I department (research@uhbristol.nhs.uk; 0117 342 0233) as required.

6.2 Laboratory medicine authorisations to support research

- All relevant information regarding the specific laboratory requirements of the research study must be provided to the laboratory during study set up. This includes but is not limited to the following:
    - Latest version of the protocol (may be pending sponsor/ethical approval if study is in setup)
    - Normal/reference ranges for required laboratory tests (if research specific)
    - If results fall outside normal/reference ranges, process in place for rapidly disseminating results to relevant personnel and ensuring review and action take place
    - Expectations of how samples will be received at the laboratory (frequency, any specific temperature requirements)
    - Instructions on required sample storage arrangements and archiving requirements of both the samples and the data generated as applicable
    - Funding arrangements
- Authorisation from the relevant laboratory department at UH Bristol or North Bristol as applicable to support the research study must be in place prior to commencement of the research study by completion of the relevant 'lab pro-forma'. These pro-formas are standalone templates in the UH Bristol R&I Quality Management System and latest versions are provided on the website (or can be accessed by contacting R&I directly). This completed authorisation must be stored within the Investigator Site File and R&I department at UH Bristol. A process must also be put in place during study set up to describe how updates to study documentation are to be disseminated to relevant laboratory staff e.g. updated protocol, study end date extension, changes to required laboratory tests. If the laboratory is unable to implement the changes to the study a discussion with the PI and Sponsor must take place immediately and any required actions must be put in place and documented appropriately; for example, amendment not implemented, study halted to recruitment.
- It is important that activities which would not take place as part of usual clinical care – i.e. those required just for the purposes of research - are captured within the laboratory pro-forma, as well as special research requirements for routinely collected samples. The financial arrangements must also be detailed in the pro-forma. Advice regarding the pro-formas can be obtained from lab medicine or the R&I team.

6.3 Engagement with external laboratories

- Where UH Bristol laboratory is unable to support the research an alternative laboratory may be sought. It is the responsibility of the Chief Investigator to ensure and to document that the external laboratory:
    - Has certification and accreditation. Where none exists a documented discussion to take place with Sponsor regarding whether laboratory meets required standards
    - is able to carry out the requirements of the approved research protocol
    - has a robust internal quality system that can assure validity of tests
    - has adequate facilities and an appropriate number of trained and qualified staff in place for the duration of the research
- Once a decision has been made to select an appropriate external laboratory, a written agreement between UH Bristol and the laboratory should be arranged and the decision documented in accordance with SOP_016 Research Contracts and Vendor Selection. It should be documented within this agreement that the laboratory agrees to work to the required regulations for the research study (i.e. SI 2004/1031 for CTIMPs) and GLP. This agreement must also detail how the laboratory will be given access to the latest version of the protocol and notified of any changes to any laboratory requirements or study processes. If the selected laboratory needs to subcontract any of the work this must be agreed with the

Sponsor and appropriate contractual arrangements with the subcontracted organisation put in place.

6.4 Laboratory SOPs

- UH Bristol laboratory departments provide an extensive clinical service across the Trust and the purpose of this document is not to describe the different processes required for that service or any other service provided by an external laboratory unrelated to UH Bristol research. The development and control of SOPs relating to clinical work/other services will therefore remain the responsibility of the laboratory departments. If there are however any conflicts between the processes described in this document and the existing laboratory SOPs, relevant laboratory staff must inform the R&I department immediately and assist in revision of the documentation.

6.5 Expected research standards

- Any laboratory work carried out for the purposes of a research study must be done in accordance with SI 2004/1031 regulations (and any amendments) where applicable (e.g. for CTIMPs), the latest version of the research protocol, participant consent, GCP and the laboratory's internal quality management system. Where specific laboratory procedures are required for a study which are not covered by or are different to the laboratories existing internal operating procedures a study specific SOP must be written, controlled, reviewed and cover all required key activities.
- Sample analysis should be performed in accordance with a predefined plan. Where this is not detailed in the protocol or is additional to routine clinical data a written procedure should be created and agreed between the Sponsor and laboratory undertaking the analysis.

6.5.1 Blinded research

- Laboratories should be notified during study set up of any blinding requirements including which personnel must be blinded throughout the study. Laboratory staff must ensure that they take appropriate measures to ensure the blind is not compromised. Should this occur, the laboratories must inform the PI and sponsor immediately.

6.5.2 Sample receipt, identification and transfer

- Laboratory staff should ensure that on receipt of any samples they are in the expected condition according to the research protocol requirements. They must also document whether they have received the expected number of samples and whether samples are labelled appropriately. On receipt of the samples the laboratory staff should document the condition that the samples arrived in and alert the PI immediately if the samples are not in the appropriate condition/are missing or inadequately labelled. If any unexpected samples are received the PI must be contacted immediately. If any of the information provided with the sample is ambiguous (specifically, the origin or type of sample), it should not be analysed until that information has been confirmed, except where a delay impacts negatively on the sample or patient (degradation/loss). In this case, the sample should be analysed and results quarantined until the identity/source is known. If samples are to be transferred, laboratory staff must ensure the transfer is carried out in accordance with the requirements of the protocol and applicable *Material Transfer Agreement (TMPL_042)* and await positive confirmation of receipt from the organisation to whom the samples are transferred.

6.5.3 Sample storage

- The required storage conditions of research samples must be documented in the protocol, study specific SOP or other trial documentation. For 'relevant material', storage and retention requirements must be defined and complied with in accordance with the Human Tissue Act. Laboratory staff must have access to this documentation and adhere to the requirements, maintaining applicable records of storage locations and conditions for the

duration of the study. If not already part of the laboratory internal quality management system, specific monitoring of storage locations (e.g freezers) must be carried out with suitable calibrated equipment. There should be a description of what processes should be followed should a temperature excursion occur, and documentation that this has taken place (if required), should be completed and filed. At the end of the research, the samples must be destroyed or transferred to a licenced Tissue Bank in accordance with the approved REC application and HTA regulations. This should be carried out in consultation with the study sponsor. If future use is planned, appropriate patient consent and/or applicable REC approval must be in place (e.g. research or transfer to tissue bank).

6.5.4 Method validation

- Analysis of research samples should be performed in accordance with a validated method. The only exception to this is where the validation of a method is one of the study objectives and this has appropriate regulatory and ethical approval.

6.5.5 Breaches and patient safety, including dose adjustments

- Processes must be in place prior to commencement of the study to describe how deviations from the protocol or serious breaches of the protocol or GCP/GLP originating in the laboratory will be managed and reported. For definition of a serious breach, please refer to the MHRA website; https://www.gov.uk/guidance/good-clinical-practice-for-clinical-trials, or contact the R&I department. The Chief Investigator should also discuss with laboratory staff during study set up any requirements to expedite reporting of laboratory results e.g. results which affect whether dose adjustments are required; laboratory staff must ensure these are adhered to. Laboratory staff may define 'alert' values for safety concerns where results are outside the normal/reference range and laboratory staff must ensure these results are communicated rapidly to the investigator and treating clinician to ensure appropriate care of the participant in line with Trust policies and Sponsor requirements.

6.5.6 Repeat analysis

- Circumstances under which repeat analysis of research samples may be undertaken must be documented and carried out only in accordance with an applicable written procedure. Any repeat analysis carried out must be documented during the course of the trial providing an explanation for the repeat results and why a specific result is accepted as the correct one. This documentation must be kept within both the laboratory files and trial master file in case reconstruction of data is required.

6.5.7 Consent

- Any laboratory work undertaken must be in line with the provision of informed consent provided by a research participant or their legal representative. The Sponsor, CI and PI are all responsible in ensuring the laboratory work is in compliance with consent and only appropriate samples are sent to the laboratory for processing. If consent is withdrawn the laboratory must be informed by the research team or Sponsor immediately and appropriate actions taken depending on the nature of the withdrawal.
- Patient confidentiality must be maintained at all times and in accordance with the patient consent. If laboratory staff receive identifiable data in error, they must immediately inform the PI and Sponsor, ensure no further disclosure of the identifiable information and follow instruction from the Sponsor of remedial actions.

6.6 Validity of laboratory data

- It is integral to the research study that the data generated by the laboratory are valid and credible. Therefore if the laboratory does not perform regular Quality Control checks of its processes these should be set up for each specific study to ensure validity of research data. Any changes made to data generated by the laboratory, the reason for the changes, when,

and by whom they were made must be documented clearly. If the data are created electronically an audit trail within the electronic system must be maintained. It is also essential that source laboratory data are identified at the study start and agreed with sponsor how laboratory data is to be reported. In addition to laboratory QC checks the Research & Innovation department will monitor UH Bristol laboratories for Quality Assurance purposes. Please refer to SOP_010 Monitoring & Oversight of Research Activity for further information.

6.6.1 Computer System Validation (CSV)

- Any computer systems implemented within the lab solely for the purposes of research must be validated prior to using them, and this must be checked periodically during use to ensure they are fit for purpose. Further information on CSV requirements can be found in SOP_011 Validation & Backup of Computer Systems used in Research.

6.6.2 Laboratory equipment

- If a laboratory is required to use specific equipment solely for the purposes of a research study (i.e. non-standard laboratory equipment), the equipment must be maintained to ensure it is performing its required function. Service contracts with the equipment manufacturer or a maintenance company must be put in place to ensure that the equipment operates according to its intended purpose. If maintenance is carried out by staff within the laboratory itself it is essential that the staff are appropriately trained and that this is adequately documented. Records of any maintenance, calibration and servicing must be kept. Prior to agreeing to host a new piece of equipment that will be subject to a maintenance contract, the PI should ensure, in discussion with the laboratory manager, that funding is in place to support the contract.
- If not already captured within a laboratory's own quality management system, general lab equipment (centrifuges, refrigerators etc) should undergo periodic calibration by appropriately qualified technicians to ensure equipment is fit for purpose. Any checks carried out must be documented.

6.7 Laboratory essential documents

- For each research study requiring UH Bristol laboratory's involvement or an externally sourced laboratory it is essential that laboratory staff maintain records relating to the research study including but not limited to;
    - latest version of protocol and any amendments
    - delegation log of laboratory staff with assigned tasks
    - documented qualifications of laboratory staff (this may be held centrally to cover more than one study if appropriate – see SOP_007 Research Training)
    - study specific laboratory procedure documentation (as applicable)
    - documentation of quality control checks
    - documentation of equipment maintenance and checks (again can be held centrally if part of laboratory's internal quality management system)
    - sample log including storage location and destruction details
- The records maintained within the laboratory should enable the laboratory work to be reconstructed at any point as required and to demonstrate the quality of the work undertaken.

6.7.1 Archiving

- If a laboratory is storing any research data (including source data), agreement about the details of the storage arrangements for that data, including location and duration must be made with the Sponsor. This can be documented in a contract or other written agreement if applicable and arrangements must be adhered to.

7. Dissemination and training in the SOP

This SOP will be disseminated to applicable research staff (including R&I) and will be available on the R&I website.

All staff whose activities are subject to this SOP should ensure that they read and understand the content of the SOP. The personal training log of the individual (and the Investigator Site File/Trial Master File if required) should be completed to document that the content of this SOP has been read and understood as described in SOP 007 Research Training.

8. Related documents

- Medicines for Human Use (Clinical Trials) Regulations 2004 (and any amendments)
- Good Clinical Practice
- Good Laboratory Practice
- Human Tissue Act 2004
- SOP_007 Research Training
- SOP_010 Monitoring & Oversight of Research
- SOP_ 011 Validation & Backup of Computer Systems used in Research
- SOP_016 Research Contracts & Vendor Selection
- TMPL_042 Material transfer agreement