UNIVERSITY OF LEEDS / NHS The Leeds Teaching Hospitals NHS Trust Standard Operating Procedure	Title	*LTHT / UoL Sample Management for CTIMPs*				
	Scope	Describes the process for the collection and management of clinical trial samples for endpoint analysis.				
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Distribution & Storage:

Distribution to:

Investigators and all members of research teams conducting or assisting with a CTIMP trial sponsored by the University of Leeds or Leeds Teaching Hospital NHS Trust.

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Contents

Section A: Introduction 4

Section B: Applicability 4

Section C: Laboratory Set-Up for CTIMP's 4

1. **Sample Type 5**
2. **Contracts 5**
3. **Training 6**
4. **Laboratory Methodologies 6**

Section D: Sample Management for CTIMP's 6

1. **The Laboratory TMF 7**
2. **Sample Collection and Consent 7**
3. **Sample Transport 8**
4. **Sample Receipt 8**
5. **Sample Processing 8**
6. **Sample Storage 9**
7. **Laboratory Equipment 9**
8. **Data Handling and Reporting 9**
9. **Quality Control 10**
10. **Quality Assurance and Compliance 10**
11. **Blinding / Unblinding (if applicable) 10**

Section E: End of Trial Procedures for Trial Samples 10

1. **Archiving 10**
2. **Sample Destruction 10**

Section F: References 11

Section G: Acronyms 11

Section H: Previous versions of Document 11

Please note: *This SOP should be used and followed in conjunction with other UoL / LTHT SOPs developed for researchers to support study set up and management. These can be found on the LTHT website or by contacting R&I / QA directly. For clinical trials where Leeds is not the trial Sponsor, please refer to any Sponsor SOPs for further information.*

Section A: Introduction

1. This Standard Operating Procedure (SOP) acts as a guide for researchers and staff to aid with sample and laboratory management when conducting non-Clinical Trial Unit (CTU)/ Contract Research Organsiation (CRO) Clinical Trial of an Investigational Medicinal Product (CTIMP's) sponsored by The Leeds Teaching Hospitals NHS Trust (LTHT) or the University of Leeds (UoL).

2. Appropriate collection and management of samples is essential for evaluation and validation of clinical findings, observations, and other activities during a clinical trial. The analysis of clinical samples which contributes to CTIMP endpoint analysis is regulated by the Medicines and Healthcare products Regulatory Agency (MHRA) and is subject to routine inspection. Analysis must adhere to the principles of Good Clinical Practice (GCP) or Good Laboratory Practice (if appropriate) at all times to ensure patient safety is not compromised and that all data is robust and accurately reported.

3. This SOP serves to ensure quality by requesting that all samples are collected, stored, and analysed as per the laboratories own Quality Management System (QMS) in a demonstrable manner, such that high quality data generated can be confirmed by audit and inspection.

4. This SOP will also describe the minimum expectations on how to collect and process samples consistently and how equipment and processes should be maintained to ensure high quality outcomes.

Section B: Applicability

1. This SOP is applicable to staff involved in the set-up of research studies and all laboratory personnel responsible for performing endpoint analysis on clinical specimens for non CTU/CRO CTIMPs sponsored by LTHT / UoL.

Section C: Laboratory Set-Up for CTIMP's

Both the Sponsor and Chief Investigator (CI) have an overall duty to ensure endpoint analysis is compliant to the principles of GCP. During trial set-up, it must be clear what is expected of the laboratory prior to undertaking any analysis.

A laboratory delegate may assume responsibility for the conduct and reporting of endpoint data for the duration of the trial. It is the laboratory delegates responsibility to ensure that all work is compliant with the regulations, to ensure analysis is conducted in line with the protocol, to adhere to a robust QMS and be a specific point of contact for all trial enquiries.

The following sections outline the minimum expectations of laboratory set-up for non CTU/CRO UoL/LTHT sponsored CTIMPs:

1. Sample Type

1.1 When setting up where trial samples are to be collected and analysed it is important to clearly define the sample type. Samples collected within a CTIMP primarily fall into one of the main categories:

- Samples collected for routine (standard care) analysis that contribute to the trial dataset.
- Samples collected for specific trial related analysis only.
- Samples prepared and stored before shipment to a third party laboratory.
- Samples analysed using an experimental assay.

1.2 All relevant information regarding sample type, collection, analysis, and storage should be clearly described within the protocol. The sample type will guide the laboratory set-up process (i.e. knowing which type of laboratory contacts will be required – please see ***Section 2: 'Contracts'***)

1.3 This SOP may not be applicable to samples analysed in a hospital environment for routine (standard of care) analysis. Please refer to the laboratories internal QMS for more information regarding samples collection, receipt etc. All clinical reference ranges must however be filed within the main Trial Master File (TMF).

2. Contracts

2.1 Contractual agreements must be signed and in place between the sponsoring organisation / institution managing the trial, and the laboratory responsible for the endpoint analysis prior to initiating any laboratory work and/or before the trial recruits any participants.

2.2 A contract outlining the roles and responsibilities of each individual party involved in the research is **not** required for analytical work taking place within the host sponsor organisation. In those instances, contracts such as a Memorandum of Understanding (MoU) should be used to outline the minimum requirements expected of the laboratory and the work expected (e.g. all work to be conducted to GCP standards).

2.3 If analysis intends to be sub-contracted to a third party laboratory, this must be discussed with Sponsor QA in the first instance. A risk assessment may be required prior to the exchange of contracts should the third party not have conducted any clinical trial work previously. At a minimum, these contacts must stipulate the standards expected of these laboratories (e.g. GCP) and clearly state the nature of the work to be undertaken.

2.4 For further information regarding laboratory contracts for University of Leeds sponsored trials, please see the University of Leeds Policy Document ***– GCP Requirements within the Laboratory'***.

3. Training

3.1 All laboratory personnel must be suitably educated, experienced and have received the appropriate laboratory training prior to commencing analysis on trial samples.

3.2 All laboratory personnel must be fully trained and aware of their specific roles and responsibilities within the laboratory environment to ensure that the data collected Is robust

3.3 A valid GCP certificate for each member of the laboratory team must be held prior to commencing any endpoint analysis. Refresher training must be completed as per local policy to ensure personnel are updated with the latest regulations and procedures.

3.4 Training records must be maintained throughout the duration of the CTIMP outlining key training and competencies. This should be kept up-to-date at all times and filed within the appropriate sections of the Laboratory TMF.**Laboratory Methodologies**

4.1 The current, approved protocol (or as a minimum, the specific sections relevant to sample analysis), must be available to the laboratory team prior to commencing any trial specific analysis.

4.2 All trial specific procedures must be documented within either the trial protocol, SOP's/Work Instruction (WI) or laboratory contract. These should contain sufficient detail to ensure the accurate reconstruction of techniques used to perform all necessary analysis. Laboratories should only perform the analysis as specified within the protocol.

4.3 All proposed amendments to the trial processes that affect the way endpoint analysis is conducted must be communicated to the laboratory team by the research team prior to regulatory submission **(*please see 'QCRES_03_Researchers guide to Notification of Amendments for UoL LTHT Sponsored CTIMP's' for further details regarding amendments*).** These amendments must be assessed by the nominated laboratory delegate prior to implementation to ensure trial work is still feasible within the laboratory**.** All documentation and communications must be filed within the appropriate section of the Laboratory TMF (***please see for Section D for further information***).

4.4 Any deviations from the protocol mandated analysis must be reported to Sponsor Quality Assurance (QA) immediately as per the process outlined in ***QCRES02: Researchers Guide to Protocol Deviations, Violations and Potential GCP Breaches'***

Section D: Sample Management for CTIMP's

A robust QMS should be in place in all laboratories managing clinical trial samples to provide a level of assurance for the Sponsor that all analysis is compliant with the protocol and relevant regulations (i.e. GCP, Medicines for Human Use 2004). Whilst each laboratory will differ in some aspects of their operation and management, it is essential that all endpoint laboratory analysis must be performed as outlined in the trial protocol to the relevant regulatory standards.

The following sections outline some examples of the minimum requirements expected of each laboratory QMS for endpoint analysis on human samples for CTIMP's sponsored by LTHT/UoL:
(Please note: this list is not exhaustive).

1. The Laboratory TMF

1.1 Key documentation and correspondence must be filed and held within the Laboratory TMF for the duration of the clinical trial. Examples include (but are not restricted to):

a. Current and any superseded versions of the protocol (or the relevant sections).
b. All applicable trial amendment documentation including correspondence, acknowledgement letters and approval letters.
c. Delegation of Duty logs
d. Qualifications of all laboratory personnel assigned to perform trial duties
e. Study specific SOP's / WI's
f. Maintenance Records
g. Sample Logs (including sample receipt and tracking).
h. Documentation evidencing consent for all samples received.
i. Documentation relating to the withdrawal of consent
j. Evidence of correspondence relating to any key decisions.
k. Reference Ranges (if applicable)

2. Sample Collection and Consent

2.1 Consent must be obtained from the participant as per the trial specific protocol and regulatory guidelines prior to any sample collection or analysis.

2.2 Samples must be collected as described in the protocol, patient information sheet (PIS) and informed consent document.

2.3 Evidence of consent should be clearly documented on the sample documentation upon receipt of the samples into the laboratory. If evidence of consent is not clearly documented at the time of receipt, this must be confirmed prior to any analysis taking place.

2.4 A documented procedure must be in place and implemented in full in the event that a participant withdraws consent (either for trial samples or trial data).

2.5 All samples should be appropriately labelled, ensuring no patient identifiable information is documented on the trial specimen tubes (this may not apply in a hospital setting where samples are taken as "standard of care").

2.6 An example of sample labelling should specify the following:

- Trial Identification
- Subject Identification
- Date/Time of Collection

- Trail Visit Number/Timepoint
- Type of specimen

3. Sample Transport

3.1 Samples must be transported to the laboratory in such a way that their integrity and viability remains unaffected.

3.2 Samples collected for routine "standard of care" analysis should be processed and transported to local laboratories in line with local procedures.

3.3 Samples being transported to a third party location must be collected, packaged, and transported as outlined within the protocol. If the protocol is unclear, reference should be made to the contractual agreement to establish the mode of transport.

3.4 If a courier is needed to transport samples, evidence of transport including collection, delivery confirmation and temperature records (if applicable) should be retained within the relevant section of the Laboratory TMF.

4. Sample Receipt

4.1 Laboratories should have robust systems in place to receive and process samples in a timely and efficient manner to preserve the integrity and viability of each sample.

4.2 At a minimum, all samples received in the laboratory should be inspected upon receipt to ensure that the physical integrity remains intact. Samples that look to have been compromised during transit should be investigated prior to analysis unless a delay would further compromise the integrity of the sample. In this instance, the sample should be analysed, and the result quarantined until investigations have concluded and there is a clear outcome.

4.3 Should problems not be able to be resolved, or if there are any further concerns, please escalate to the Sponsor as soon as possible.

4.4 All sample receipt information detailing key information such as date and time of receipt, the number of samples received, and trial identifiers should be held within the relevant section of the Laboratory TMF.

5. Sample Processing

5.1 Documented systems and processes (often in the form of SOPs or WI's) should be in situ within the laboratories detailing how samples are processed and the equipment used to support this activity. These should be reviewed periodically and updated should changes in processes arise.

5.2 In the event of an inspection, all relevant information regarding the sample tracking history must be provided including records of how it was transported and where it was stored in order to ensure a full audit trail of each sample.

6. Sample Storage

6.1 Storage areas housing clinical trial samples must always be monitored to ensure that the sample has been stored appropriately and sample integrity is maintained.

6.2 Any fridges or freezers that store trial samples must hold an appropriate log of regular temperature readings to provide assurance on the quality of the storage conditions. This can be done using an automated electronic system (i.e. Tutela), or using paper based logs.

6.3 Where appropriate, suitable alarms and back-up systems should be in place to mitigate against equipment or power failures. Any temperature variations or failures should be recorded, and Sponsor QA notified as per the processes documented in '***QCRES02: Researchers Guide to Protocol Deviations, Violations and Potential GCP Breaches'.***

7. Laboratory Equipment

7.1 All laboratory equipment, including computerised systems and software should be fit-for purpose. Procedures such as servicing, calibration, maintenance, and validation should be performed in accordance with the laboratories overarching QMS.

7.2 Clear records of servicing and calibration checks should be available upon audit / inspection and maintained within the Laboratory TMF.

8. Data Handling and Reporting

8.1 Information such as dates, times, reagent batch numbers, signatures must be legible and accurate to ensure traceability at all times. All data should be recorded accurately and promptly.

8.2 Data produced in laboratories may be termed 'raw' or 'source' data and appropriate steps must be taken to ensure that this data is stored within the Laboratory TMF for the duration of the trial and for the specified retention period (please ***see Section E: Archiving*** for further information regarding the long-term storage of laboratory data).

8.3 A 'Data Management Plan' is required to be created during trial set up for all single site trials. This plan should detail key information such as the storage and location of all raw/source data and specify the required retention period. ***Please see 'QCRES_07: A Researchers Guide to Data Management' for further information.***

8.4 All sample related data should be appropriately anonymised so as not to breach patient confidentiality and GDPR regulations.

9. Quality Control

9.1 The laboratory performing endpoint analysis may have accreditation (i.e. ISO15189) which in turn should describe the QA and Quality Control (QC) processes within the laboratory.

9.2 The accuracy of all lab processes should be subject to a proportionate level of QC. Sufficient detail must be provided within the laboratories QMS regarding the checking and validation of sample results including procedures relating to sample reanalysis (where required).

10. Quality Assurance and Compliance

10.1 Compliance will be assessed against this SOP by Sponsor QA periodically or as per the trial specific monitoring plan. Evidence of a fully operational QMS will be reviewed to ensure that samples are managed correctly, GCP principles are being adhered to, patient safety is not compromised, and that data is robust and accurately reported.

11. Blinding / Unblinding (if applicable)

11.1 Maintaining the integrity of the blind is an essential component of a clinical trial. The compromise of a study blind can have a major impact on data integrity of the trial.

11.2 Processes documented within the laboratory QMS should detail the measures taken within the laboratory environment to ensure laboratory personnel do not inadvertently compromise the blind.

Section E: End of Trial Procedures for Trial Samples

1. Archiving

1.1 The laboratory TMF is usually archived alongside the main TMF unless otherwise specified. This enables the full trial to be reconstructed if necessary. Please liaise with the research team when planning and preparing to archive the Laboratory TMF.

1.2 An archived laboratory TMF should be retained in accordance with the retention period specified within the trial protocol.

2. Sample Destruction

2.1 At the end of the clinical trial, samples may be marked for destruction, or transferred to long term storage (this should be described within the study protocol).

2.2 If samples are to be destroyed, a specific process must be in place to ensure this is done safely and accurately. The complete audit trail of this process must be maintained.

Section F: References

MHRA Good Clinical Practice Guide 2012
The Medicines for Human Use (Clinical Trials) Regulations 2004
E6 International Guideline for Good Clinical Practice (2011) - *Version 2.1.* Available from: https://www.ema.europa.eu/en/documents/scientific-guideline/ich-e-6-r2-guideline-good-clinical-practice-step-5_en.pdf
EMA "Reflection Paper for Laboratories that Perform the Analysis or Evaluation of Clinical Trial Samples" (2012) - *EMA/INS/GCP/532137/2010.* Available from: https://www.ema.europa.eu/en/documents/regulatory-procedural-guideline/reflection-paper-laboratories-perform-analysis-evaluation-clinical-trial-samples_en.pdf
Good Clinical Practice within the Laboratory - University of Leeds Policy Document.
QCRES_07: A Researchers Guide to Data Management
QCRES_02: Researchers Guide to Protocol Deviations Violations and Potential GCP Breaches
QCRES_03: Researchers Guide to Notification of Amendments for UoL/LTHT Sponsored CTIMPs

Section G: Acronyms

CI	Chief Investigator
CTIMP	Clinical Trial of an Investigational Medicinal Product
CRO	Contract Research Organisation
CTU	Clinical Trials Unit
GCP	Good Clinical Practice
LTHT	Leeds Teaching Hospitals NHS Trust
MHRA	Medicines and Healthcare products Regulatory Agency
MoU	Memorandum of Understanding
PIS	Patient Information Sheet
QMS	Quality Management System
QC	Quality Control
QA	Quality Assurance
SOP	Standard Operation Procedure
TMF	Trial Master File
UoL	University of Leeds
WI	Work Instruction

Section H: Previous versions of Document

Version no.	Valid from	Approved by	Date approved
1.1	10/01/2014	Neville Young	10/01/2014