Technology, Infrastructure and Environment Directorate Clinical Research Governance Team

Standard Operating Procedure

Requirements for CTIMPs not being managed by a CTU

SOP003

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1. Introduction

The Medicines for Human Use (Clinical Trials) (Amendment) Regulations 2025 (the Regulations) set out the responsibilities and functions that must be undertaken by a Sponsor or on behalf of a Sponsor in the conduct of Clinical Trials of Investigational Medicinal Products (CTIMPs) within the UK.

Where the University of Liverpool (University) undertakes the role of Sponsor for a CTIMP the study team is required to detail the Clinical Trials Unit (CTU) that will undertake study management functions on behalf of the University, or where a CTU is not being used, the quality system that the CTIMP will be run within. If a CTIMP is to be run without a CTU, the reason for this must be justified at the point of Sponsorship application. This procedure should also be referred to when planning a Clinical Investigation of Medical Device (CIMD) which are regulated by the Medical Devices Regulations 2002. Scope of Procedure

This SOP describes the requirements that non-CTU managed CTIMPs and CIMD must meet in order to ensure appropriate undertaking of Sponsor delegated functions.

2. Who

This SOP is relevant to staff within the Technology, Infrastructure and Environment Directorate Clinical Research Governance Team, members of the University Clinical Research Regulatory Oversight Committee (CRROC) and members of the Liverpool Health Partners (LHP) Joint Research Office Committee (JRO) Sponsorship Committee.

It is also relevant to Chief Investigators, students, trial coordinators and other members of University Staff involved in undertaking a CTIMP or CIMD not being managed by a CTU.

3. When

This SOP should be referred to during the setup and conduct of a CTIMP and CIMD not being managed by a CTU.

4. Procedures

The Regulations details the Sponsor responsibilities for CTIMPs. When the University is undertaking the role of Sponsor for a CTIMP it is expected that a CTU is contracted to undertake delegated functions on behalf of the University[1]. It is recognised, however, that the use of a CTU is not always appropriate for some CTIMPs and the following sections describe the requirements for non-CTU Managed CTIMPs. In all circumstances where a CTIMP is being managed outside of CTU it is required that TEM022[2] is completed and signed off by relevant parties. This template will be released by the Clinical Research Governance Team at the earliest time point to ensure prompt completion.

[1] See also POL002 Clinical Trials of Investigational Medicinal Products Sponsored by the University Statement of Policy
[2] Non CTU Sole Sponsorship Internal Delegation Plan

Quality System

All CTIMPs must be conducted within the remit of a robust quality system that defines the Standard Operating Procedures (SOPs) that will be used throughout the set-up, conduct and completion of a CTIMP. These SOPs must set out the standards and regulations that are to be adhered to and defines how these standards will be met. The quality system may also include policies, manuals, handbooks, records and templates.

The University expects all CTIMPs to have a quality system in place that complies with the Regulations. If there are any other regulations that specifically apply to the trial, for example The Medical Devices Regulations 2002, The Human Tissue Act 2004, or the Mental Capacity Act 2005, this must be stated in the quality system, and relevant procedures must be in place to ensure compliance with these regulations.

Prior to the start of a trial the CI must identify which quality system will be used during the conduct of the trial and the quality system to be used may depend on the organisational structure or the size and complexity of the trial.

It may be applicable to use one of the following types of quality systems:

- CTU Quality System
- NHS Trust Quality System
- Trial Specific Quality System

In the case of a single investigator conducting a single trial, the quality system requirements below may be incorporated into the trial protocol, ensuring that all trial specific procedures to be followed are detailed. This is where a complex quality system would not add value, but it must be discussed with the Senior Clinical Research Governance Manager and will be subject to review and approval as part of a Vendor Selection Audit under SOP025[3]

For CTIMPs being conducted at International sites the quality system to be used may be that of the lead research site. It is noted here that the Senior Clinical Research Governance Manager may undertake a Vendor Selection audit of the quality system to be used if it is provided by an organisation that the University has not recently worked with, or if a new quality system is being developed specifically for the trial. This is to ensure adequate compliance with the required regulations, as well as appropriate reporting to Sponsor.

Each procedural document within the Quality system must be version controlled and contain information regarding the authorship, ratification, approval and review dates. The following sections detail the minimum requirements that a quality system must meet in order to conduct a CTIMP. Please note this list is not exhaustive. It is expected that each of these items will have a related SOP that details the specific procedures for each situation.

[3] Sponsor Audit

- Trial set up
- Trial Green Light
- Information systems
- Data Management
- Site Selection and site opening
- Risk Assessment
- Modifications
- Monitoring
- Identification and Notification of Serious Breaches
- Safety Reporting
- Urgent Safety Measures
- Training
- Annual Reporting to MHRA (DSUR)
- Delegation of Study Responsibilities
- Bi-Annual Reporting to Sponsor
- Maintaining the Trial Master File
- End of Study
- Maintaining an Investigator Site File
- Archiving

Trial set up and Trial Green Light

There should be a documented process for ensuring that all required approvals, contracts, confirmation of capacity, and necessary documentation are in place. Records must be available to verify that all required documents have been received before the trial can commence. This process is referred to as the 'Trial Green Light'. Sponsor can advise on the required documentation using the Sponsor Permission to Proceed Checklist

Site Selection and site opening

In line with the Trial Green Light process there should also be a defined process for identifying and selecting sites and progressing sites to opening.

Site selection should consider the capacity and capability of the site to recruit the required participant demographic as well as the ability to deliver the trial requirements in relation to both clinical delivery of the trial such as appropriate medical cover and appropriate levels of required staff, and nonclinical activities such as completion of case report forms (CRF) and maintenance of the Investigator Site File (ISF).

Before a site opens to recruitment is expected that a Site Initiation Visit is conducted ensure the site research team are appropriately trained on the protocol, specific procedures, data collection tools and any study specific equipment. This can be carried out either face-to-face or remotely, but consideration should be given to the requirement to visit site facilities, such as a laboratory.

Data Management

Data management covers the entire duration of a CTIMP, and documented processes should be implemented. A Data Management Plan should be produced and include details on the following areas;

- The design and production of the data capture tool for collection of participant data at participating sites (whether paper, electronic or hybrid)
- The design, construction and maintenance of the database for the trial. Consideration should be given to the type of database used, e.g. Microsoft Excel or Access are not an accepted CTIMP databases, as they offer no means to audit any changes and may pose security risks. The Senior Clinical Research Governance Manager can provide support and advise on suitable databases
- How data will be processed including entry, cleaning and queries
- Where Quality Control (QC) checks are required and how these are undertaken and documented
- Production of the final dataset(s) for analysis and the process for "data lock"
- Training of staff involved in data collection and data management

The University Research Data Management Team can provide further advice on Data Management arrangements.

Computer Systems Validation and Information systems

All information and computer systems used in CTIMPs should be subject to a documented validation process to demonstrate that the system and its use for the trial are fit for purpose. This is particularly important for systems that impact the quality of the trial data and safety of participants. There are three key principles for validation;

- Appropriate controls of the system are in place throughout the systems lifetime
- Documentation is available to support the application and use of the controls
- The system is fit for purpose and performs reliably and consistently as intended.

Risk Assessment

All University sponsored CTIMPs are required to undergo a risk assessment. The Risk assessment must be carried out as early as possible to ensure measures are taken to minimise the risks and potential hazards and to consider these risks whilst writing the study protocol. The risk associated with the IMP should also determine the trial procedures for monitoring the safety of participants.

The University requires a Risk Assessment Procedure to be in place outlining the process, roles, responsibilities and record keeping requirements for carrying out study specific risk assessments. The procedure should be developed in accordance with the MHRA/ DH/MRC Joint Project "Risk-adapted Approaches to the Management of Clinical Trials of Investigational Medicinal Products".

Monitoring

Monitoring is required for all University sponsored CTIMPs and a procedure should be in place to assess the extent and level of monitoring to be carried out in accordance with the study specific risk assessment. This assessment should then be documented in a monitoring plan, which should also state whether monitoring activities:

- Are delegated to the CI.
- Are completed by the recruiting sites, or an external organisation, such as a Contract Research Organisation (CRO). In this event the process for monitoring will be reviewed to assess suitability. If the process is not suitable alternative arrangements must be made.
- Cannot be completed by the CI, University or other organisation. Under these circumstances the study may be rejected by the JRO Sponsorship Committee if the regulatory requirements cannot be met.

The monitoring plan will also outline the criteria for the following monitoring activities and definition of when these are to be carried out in the trial, to ensure that the Regulations are complied with:

- Day to day monitoring
- Central monitoring
- On-site monitoring

Further information on the requirements for monitoring can be found in SOP011.

Safety Reporting

The University requires that there are clear procedures in place for all aspects of safety reporting for CTIMPs to ensure that the requirements described in Part 5 of The Medicines for Human Use (Clinical Trials) (Amendment) Regulations 2025 are complied with. Safety reporting is documented in the regulations as being the responsibility of the sponsor; however, this is delegated to the CI or the CTU managing the trial.

As a minimum, procedures for safety reporting should include the following:

- The requirement to keep records of all adverse events (this may depend on the trial and the protocol requirements).
- Definition of the roles and responsibilities for assessing the expectedness and seriousness of any adverse events and whether they are directly related to the IMP.
- The process for reporting serious adverse events (SAEs) or reactions (SARs) to the sponsor within 24 hours, including the arrangements to ensure sufficient cover for timely processing of SAEs.
- The requirement to provide a detailed report all of serious adverse events or reactions to the sponsor following the initial notification.

- The definition of the roles and responsibilities for reporting Suspected Unexpected Serious Adverse Reactions (SUSARs) in accordance with the requirements of the Regulations.
- The requirement to produce an annual report including all suspected serious adverse reactions (including all SUSARs) and a summary report of the subject's safety.

Further information on the requirements for safety reporting be found in SOP007.

Training

The Regulations require that *"Each individual involved in conducting a trial shall be qualified by education, training and experience to perform his tasks."* In order to demonstrate that training has occurred for all staff involved in the conduct and reporting of CTIMPs and, where appropriate, for staff involved in supporting function procedures should be in place outlining the training arrangements in place, the roles and responsibilities and the maintenance and location of the related documentation. The University requires the following documentation to be retained in order to demonstrate training:

- A current job description dated and signed by the post holder and their line manager to demonstrate the date on which current roles and responsibilities have been agreed.
- Curriculum Vitae to demonstrate current and previous relevant education and experience signed and dated to confirm the date of the document and ownership by the named individual. This should be updated at least every 3 years.
- Confirmation that Good Clinical Practice (GCP) training has taken place within the last **3 years.**
- Records of role specific and SOP training.

Delegation of Study Responsibilities

A procedure should be put in place that details the delegation of study responsibilities that includes overall study responsibilities such as application for REC and Clinical Trials Authorisation (CTA) from the Medicines & Healthcare products Regulatory Agency (MHRA) and maintenance of the Trial Master file, as well as the creation of a delegation log for trial sites. Overall trial responsibilities will be delegated either in a Co-Sponsorship Agreement or in the Internal Delegation Plan.

A delegation plan is required for each recruiting site to detail which members of the trial team will undertake which function in relation to the trial. This plan has to be signed by the PI who formally delegates the responsibilities. Responsibilities may include[4];

- Assessment of Eligibility Criteria
- Review of Medical history
- Adverse Reaction Sign Off
- CRF Completion

[4] The list is not exhaustive and should be amended according to the trial protocol.

- Obtaining Informed Consent
- Randomisation
- Obtaining contact details
- Allocation of Trial Treatment
- Sample Collection
- Adverse Reaction CRF completion
- SAE reporting
- CRF sign off
- Photocopy and post of CRF forms
- Photocopy of seizure diaries
- Issue of baseline questionnaires
- Site File Maintenance
- Contacting the GP

Further information on the requirements for delegation of duties can be found in SOP006.

Maintaining a Trial Master File (TMF)

There must be a procedure in place detail the creation and maintenance of the TMF. The Sponsor is responsible for maintaining the TMF, but this function will be delegated to the CI who then may delegate to a further member of study team. The procedure should detail the essential documents to be held and the security of the TMF. The University requires that all TMFs are held as paper records and although electronic records may be used to supplement the paper TMF all documents must be available in paper format at the time of audit or inspection. If a trial team wishes to use a full electronic TMF this must be discussed with the Sponsor at the initial stages of trial set up.

Appendix C of ICH GCP E6 (R3) gives further guidance on what records should be considered essential and therefore require retention.

Further information on the requirements for TMF can be found in SOP015.

Maintaining an Investigator Site File (ISF)

Each trial site must ensure that an ISF is created and maintained throughout the study duration. This is essential to ensure oversight of the work undertaken and also permits the reconstruction of the trial. The ISF should include all source data and any transcription. A procedure must be in place to detail the documents required to be retained for the trial and procedures for storage and archiving. The procedure should also detail who is responsible for the initial creation of the ISF.

Modifications

All Modifications to protocol, study documentation or management arrangements for a study must be reviewed and approved by the Sponsor(s) **prior** to the amendment being submitted to REC and MHRA where appropriate. When reviewing any Modifications, the Sponsor will assess substantiality of the amendment and provide advice on the approvals required prior to implementation of the Modification. A procedure must be in place to ensure that the Sponsor is given the opportunity to review each Modification, and it must detail the process for submission to appropriate regulatory bodies and recruiting sites.

Further information on the requirements for Modifications can be found in SOP018.

Identification and Notification of Serious Breaches

The Regulations define a serious breach as an event which is likely to affect the safety or physical or mental integrity of the subjects of the trial or the scientific value of the trial.

Under the Regulations the sponsor is responsible for the reporting of the serious breach to the licensing authority (MHRA) within 7 days. This responsibility is delegated to the CI.

The University requires documented procedures to be in place to:

- Define the process for assessing the classification of a serious breach.
- Outline the responsibilities and the process for reporting of serious breaches to the sponsor.
- Explain the arrangements in place to ensure detailed records of all serious breaches are retained.

Urgent Safety Measures

An Urgent Safety Measure is an action that the Sponsor and CI may take in order to protect the subjects of a trial against any immediate hazard to their health and safety. Procedures must be in place to ensure that the MHRA and the REC are notified immediately by telephone and within 3 days in writing of the measure being taken and the reasons why. The procedures must also detail notification of the measure to the Sponsor(s). Once the measure has been implemented a substantial Modification must then be made detailing the measure.

Annual Reporting to MHRA

The MHRA require a Development Update Safety Report (DSUR) to submitted annually from the date of initial approval for the trial duration. The responsibility for the submission of these is delegated to the CI. Guidance for the submission of these is available from the MHRA rand a procedure must be in place that details the submission requirements.

End of Study

A procedure must be in place that details the definition of the end of the study, close out of trial sites and submission of end of study reports, including making the result publicly available. The procedure must detail the regulatory requirements and timeframes for reporting at the end of the trial. The procedure must also detail the process to be undertaken in the event of early termination of the trial.

Archiving

Regulation 31A of the clinical trials regulations mandates retention of essential records and participant medical files for at least 25 years from the conclusion of the trial, or longer if required for marketing authorisation purposes.. The University provides archiving for CTIMP documents with Restore Document Management Services Company. There must be a procedure in place that details the arrangements for archiving.

5. Roles and Responsibilities

The CI is responsible for ensuring CTIMPs not being managed by a CTU are run within a quality system.

The CI is also responsible for ensuring the quality system is fit for purpose.

The Sponsor is responsible for ensuring the quality system complies with the relevant regulations.

6. Abbreviations

CI	Chief Investigator
CRROC	Clinical Research Regulatory Oversight Committee
CTA	Clinical Trials Authorisation
CTIMPs	Clinical Trials of Investigational Medicinal Products
CTU	Clinical Trials Unit
DSURs	Development Update Safety Reports
GCP	Good Clinical Practice
ISF	Investigator Site File
JRO	Joint Research Office Committee
LHP	Liverpool Health Partners
MHRA	Medicines & Healthcare products Regulatory Agency
Regulations	The Medicines for Human Use (Clinical Trials) Regulations 2004
SOP	Standard Operating Procedure
TMF	Trial Master File
University	University of Liverpool

7. Associated Documents and References

This MHRA/ DH/MRC Joint Project "Risk-adapted Approaches to the Management of Clinical Trials of Investigational Medicinal Products".

POL002 Clinical Trials of Investigational Medicinal Products Sponsored by the University Statement of Policy

SOP006 Delegation of Roles and Responsibilities for University Sponsored and Co-Sponsored Studies

SOP007 Safety Reporting for University of Liverpool Sponsored CTIMPs

SOP011 Monitoring of University Sponsored CTIMPs

SOP015 Maintaining a Trial Master File for Clinical Trials of Investigational Medicinal Products (CTIMP) studies

SOP018 Procedure for the Submission of Modifications

TEM022 Non CTU Sole Sponsorship Internal Delegation Plan

8. Training and Resources

All CIs and members of trial teams for CTIMPs not being managed by a CTU must ensure they have read this SOP and understand the requirements.

9. Monitoring and Audit

The University will undertake monitoring of adherence to this SOP during the set-up of CTIMPs not being managed by a CTU.