Clinical Directorate Clinical Research Governance Team

Standard Operating Procedure

Clinical Trials of Investigational Medicinal Products Sponsored by the University

POL002

Author	**Date of Approval**
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Approved on behalf of ratifying committee	**Date of Approval**
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Document Control

Issue Date	07/03/2022
Effective Date	7th March 2022
Review Date	7th March 2024
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Document History can be viewed on Q-Pulse

Review Process Prior to Sign Off

Name of Committee	**Date**
Sponsorship Review and Approval Committee – v1	8th March 2013
Joint Research Office Sponsorship Committee – v2	7th July 2015
Joint Research Office Sponsorship Committee – v3	11th May 2017
LHP SPARK Sponsorship Committee – v4	15th February 2022

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1. Introduction

The Medicines for Human Use (Clinical Trials) Regulations 2004 (SI 2004/1031) and as amended (the Regulations), set out the requirements for implementation of Good Clinical Practice (GCP) in the conduct of Clinical Trials of Investigational Medicinal Products (CTIMPs) within the UK.

As a sponsor the University of Liverpool (hereinafter the University) has specific legal responsibilities in relation to the authorisation and conduct of CTIMPs. The University can delegate some of the functions of sponsorship, but retains ultimate responsibility for these activities. The University has implemented processes to maintain oversight of sponsored CTIMPs to ensure all legal responsibilities are met. CTIMPs can only be undertaken when there are sufficient resources to ensure that all legal requirements are met and can be delivered. The University will take this into consideration when reviewing a study for Sponsorship.

2. Purpose

This policy outlines the minimum requirements for CTIMPs sponsored by the University, in order to comply with The Medicines for Human Use (Clinical Trials) Regulations 2004.

3. Sponsorship of CTIMPs

To ensure optimal management of CTIMPs the University prefers that all CTIMP's are managed by Liverpool Clinical Trials Centre (LCTC). Where an external Clinical Trials Unit (CTU) or Contract Research Organisation (CRO) is identified to manage a CTIMP the University will undertake a Vendor Selection Audit to confirm that the CTU/CRO quality system is suitable;

- The management and coordination of large-scale Phase 3 and Phase 4 CTIMPs should be overseen by an appropriate CTU, but this will be determined on a case by case basis. Phase 1 and Phase 2 CTIMPs may not require the involvement of a CTU; however, this will be assessed during the sponsorship application procedure;
- In cases where a CTU is not identified to manage the CTIMP the University will require the CI to identify or provide the suite of Standard Operating Procedures that they intend to follow. The identified Quality Management System will be subject to a Vendor Selection Audit to ensure suitability;
- The University will usually undertake Sole Sponsorship of CTIMPs and this is assessed on a case by case basis;
- For Sole Sponsored CTIMPs managed by LCTC an Internal Delegation Plan (TEM033) will be put in place to define the functions delegated to the CTU and other University departments involved in the running or management of the CTIMP. If an external CTU is managing the CTIMP a Service Level Agreement or similar agreement will be put in place alongside an External CTU Communication Plan (TEM034);
- In the case of co-sponsored CTIMPs, the University requires a co-sponsorship agreement to be drawn up with the co-sponsoring NHS Trust, and for the co-sponsor to assume the sponsor responsibilities defined in Parts 4,5,6,7 of the Regulations (Attached as Appendix 3).

4. Pre-trial set up

The University requires various documents or processes to be in place prior to the study being considered for Sponsorship.

4.1 Appropriate sponsor

An appropriate sponsor must be confirmed prior to applications to the Health Research Authority (HRA) Research Ethics Committee (REC) and any regulatory bodies such as the Medicines & Healthcare products Regulatory Agency (MHRA). Under the Regulations the Sponsor is defined as;

"an individual, company, institution or organisation, which takes responsibility for the initiation, management and/or financing of a clinical trial."

The University Statement of Policy for Sponsorship of Research (POL001) details the circumstances when the University will act as a sponsor for a CTIMP. It is noted here that whilst covered by the definition in the Regulations the University does not allow any individuals to act as a Sponsor for CTIMPs.

Final Sponsor Permission to Proceed must be gained prior to the CTIMP opening for recruitment. This is issued upon receipt of required governance and regulatory documents which will be defined at the time of Sponsorship Approval. This process is managed by the Clinical Research Governance Team in the Clinical Directorate of the Faculty of Health and Life Sciences and further information can be found in the Sponsorship Application and Approval SOP (SOP004). If a University Sponsored CTIMP opens for recruitment prior to Sponsor Permission to Proceed being issued this may result in disciplinary action.

4.2 Protocol development

A protocol is a key trial document and all CTIMPs must have a protocol in place that adheres to the standards set out by the ICH GCP guidance (section 6);

"The contents of a trial protocol should generally include the following topics. However, site-specific information may be provided on separate protocol page(s) or added in a separate agreement, and some of the information listed below may be contained in other protocol referenced documents, such as Investigator's Brochure"

- General study information including title, version number and contact details of study team
- Background Information about the Investigational Medicinal Products (IMPs) and outcomes from previous trials or studies.
- Trial Objectives and Purpose
- Trial Design
- Selection and Withdrawal of Subjects
- Treatment of Subjects
- Assessment for Efficacy
- Assessment of Safety

- Statistics
- Direct Access to Source Data/Documents
- Ethical considerations relating to the trial
- Data Handling and Record Keeping
- Financing and Insurance
- Publication Policy

Further information and guidance are available from the Health Research Authority[1].

4.3 Scientific peer review

A scientific peer review of protocol and other key trial documentation is required in order to reduce potential errors with the trial design and conduct. Peer review should be conducted by appropriately qualified and experienced persons who are independent to the trial team to ensure that that any errors are identified and corrected prior to finalising documents. Peer review arrangements should be clearly documented along with evidence that recommendations have been assessed and incorporated.

4.4 Data Monitoring Committee

For large, multi-centre blinded CTIMPs the University expects that a Data Monitoring Committee (DMC) is established. For other trials it may be deemed appropriate for a DMC to be formed, however this will be assessed on a case by case basis.

The role of the DMC is to review and assess unblinded safety data and assess trial progress. It is imperative that the DMC has fully independent membership. The DMC reports to the Sponsor or other trial oversight committees with any recommendations relating to study modification, continuation or termination. The DAMOCLES study group (2005) have developed a standard charter for DMCs to adhere to. It states that the DMC should comprise of a small group of experts who are external to the trial. This should include at least one clinician experienced in the clinical area, and at least one statistician. The immediate study team may be asked to attend "open" sessions, but will not attend the "closed" sessions. The definition of each session should be included in the DMC Charter.

The DAMOCLES study group standard charter for DMCs includes the following sections;

a) Introduction
b) Roles and Responsibilities
c) Pre-trial
d) Composition
e) Relationships
f) Organisations
g) Trial documentation and procedures to ensure confidentiality and proper communication
h) Decision making

[1] https://www.hra.nhs.uk/planning-and-improving-research/research-planning/protocol/

i) Reporting
j) After the trial

4.5 Trial Steering Committee

For large CTIMPs it may also be necessary to establish a Trial Steering Committee (TSC). The TSC acts as a body that takes responsibility for the scientific integrity of a clinical trial and also takes responsibility for the scientific validity of the study protocol, assessment of study quality and conduct and for the scientific quality of the final study report. The TSC does not need to be an independent committee and can comprise of personnel directly involved in the trial, however the University recommends that a TSC is chaired by someone independent of both the research team and the Trial Management Group and invites further independent TSC members. The University also requests that a Sponsor representative is a member of the TSC to ensure the Sponsor is kept fully up to date of trial progress. The Sponsor will review the membership and the Terms of Reference for both the DMC and TSC to assess suitability. If the Investigator does not implement a TSC or DMC a reason for this must be provided to the Sponsorship Team who will assess if one is necessary with the Chair of the SPARK Sponsorship Committee.

4.6 HRA REC Favourable Opinion

Under the Regulations a CTIMP cannot begin and participants cannot be recruited until:

> *"an ethics committee…appointed under Schedule 4 has given a favourable opinion in relation to the clinical trial…"*

The recognised ethics committee in England is the HRA REC.

In cases where a CTIMP is managed by a CTU the function for applying for initial REC approval and for any necessary amendments will be delegated to the CTU. For CTIMPs not being managed by a CTU this function will be delegated to the CI in the first instance. All correspondence related to initial approvals and amendments should be provided to the Sponsorship Team.

4.7 MHRA Clinical Trial Authorisation (CTA)

A Clinical Trial Authorisation (CTA) must be obtained from the Competent Authority (MHRA) prior to a CTIMP commencing. In cases where a CTIMP is managed by a CTU the function for applying for initial MHRA CTA and any necessary amendments will be delegated to the CTU. For CTIMPs not being managed by a CTU this function will be delegated to the CI in the first instance. All correspondence related to initial approvals and amendments should be provided to the Sponsorship Team.

4.8 Ensure appropriate contracts are in place

The Research Contracts Team, part of the Legal and Governance department are responsible for ensuring that required contracts and agreements are in place. The Sponsorship Team will maintain oversight and receive confirmation that required contracts are in place before the start of the research. The Sponsorship Team will be guided by the Research Contracts Team with regards to the

contracts required for particular studies. The Research Contracts Team are responsible for preparation and approval of all research related contracts unless formally delegated in the Delegation of Authority. These may include;

- Agreements with funders, study collaborators and suppliers
- Confidential disclosure agreements
- Material transfer agreements
- Co-sponsorship agreements
- Research site agreements

The CI is responsible for the identification of appropriate subcontractors and for assessing their suitability. For some subcontracted functions such as the use of an external CTU the University may undertake a Vendor Selection audit prior to the supplier being formally contracted to undertake the required work. The Research Contracts Team are responsible for arranging contracts with subcontractors for CTIMPs. The CI is responsible, with support from the Sponsorship Team for managing the relationship with the subcontractor and for assessing compliance with the contract. Any Issues should be highlighted to the Sponsor Team for investigation and escalation to the University Clinical Trials Oversight Committee (CTOC).

4.9 Site Confirmation of Capacity and Capability

Site specific review must be undertaken by the Research and Development (R&D) department at each identified trial site. This must be undertaken **prior** to the trial opening for recruitment at that site. Site specific review is integrated into the normal research governance review required for each research project conducted in or through the NHS.

This process is undertaken by the Health Research Authority (HRA) under HRA Approval. HRA Approval brings together the assessment of governance and legal compliance, undertaken by dedicated HRA staff, with the independent ethical opinion by a Research Ethics Committee (REC). It replaces the need for local checks of legal compliance and related matters by each participating organisation in England. This allows participating organisations to focus their resources on assessing, arranging and confirming their capacity and capability to deliver the study. Confirmation of Capacity and Capability will be required for each trial site, alongside a signed Research Site Agreement and Organisation Information Document.

Each trial site must have an identified PI who takes responsibility for the local conduct of the trial and to who site based research staff are accountable to.

5. Quality System Requirements

A Quality System sets out the standards and regulations that are being adhered to and defines how these standards will be met. The system should define what people, actions and documents are going to be employed in order to carry out work in a consistent manner, producing evidence of what has happened. It may include policies, standard operating procedures manuals, handbooks, records and templates.

The University expects all CTIMPs to have a quality system in place that complies with the Medicines for Human Use (Clinical Trials) Regulations 2004. 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.

Depending 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:

- Clinical Trials Unit Quality System
- NHS Trust Quality System
- Sponsor Quality System
- Trial Specific Quality System

Prior to the start of a trial the CI must identify which quality system will be used during the conduct of the trial.

In order to ensure that compliance with the Regulations is incorporated into all University sponsored CTIMPs Quality Systems, the University has developed the below list of required procedures. This list of is not exhaustive and should be viewed as minimum Quality System requirements;

- Risk Assessment
- Monitoring
- Safety Reporting
- Training
- Delegation of Study Responsibilities
- Maintaining the Trial Master File
- Maintaining an Investigator Site File
- Amendments
- Identification and Notification of Serious Breaches
- Urgent Safety Measures
- Annual Reporting to REC and MHRA (DSUR)
- End of Study
- Archiving

Further guidance regarding the requirements of the above procedures is provided in the corresponding sections of this policy.

5.1 Risk Assessment

All University sponsored CTIMPs are required to undergo a risk assessment. Risk assessment must be carried out as early as possible to ensure measures are taken to minimise 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"[2].

5.2 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 to be carried out by the CTU managing the trial
- Are delegated to the CI.
- Are completed by the recruiting Trust.
- Is completed by another organisation.

Cannot be completed by the CI, University or other organisation. Under these circumstances the study may be rejected by the SPARK 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

5.3 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 SI 2004/1031 and the associated

[2] https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/343677/Risk-adapted_approaches_to_the_management_of_clinical_trials_of_investigational_medicinal_products.pdf

EU guidance are complied with. Safety reporting is documented in the regulations as being the responsibility of the sponsor; however, this is usually delegated to the CI or the CTU.

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

- The requirement to keep records of all adverse events.
- Definition of the roles and responsibilities for assessing the 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.

5.4 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, documentation must be maintained and retained for all staff involved in the conduct and reporting of CTIMPs and, where appropriate, for staff involved in supporting functions. 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.
- Confirmation that GCP training has taken place within the last **3 years.**
- Records of role specific and SOP training.

Procedures should be in place for all University sponsored CTIMPs outlining the training arrangements in place and the roles, responsibilities and location of the above records.

5.5 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, MHRA CTA and maintenance of the Trial Master file, as well as the creation of a delegation log for trial sites. Responsibilities for trial sites may include;

- Assessment of Eligibility Criteria
- Review of Medical history

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

The above list is not exhaustive and some responsibilities may need to be added, removed or amended as per the trial protocol.

5.6 Maintaining a Trial Master File (TMF)

The TMF will be held and maintained by the CI, although this may be delegated to the CTU or a member of the study team. This should be held in paper format although some records may be held electronically. The minimum documents required to be held in the TMF are detailed in the ICH GCP Guidance at Section 8 and Chapter 5 of EudraLex Clinical trials guidelines - Volume 103

5.7 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. Source data could be classed as any original document such as hospital records, clinical charts, laboratory notes, subject diaries, scan results, blood results and drug administration records. A procedure must be in place to detail the documents required to be retained for the trial and procedures for storage and archiving.

5.8 Amendments

All amendments to protocol, study documentation or management arrangements for a study must be reviewed and approved by the Sponsor to confirm suitability, substantiality and to assess which approvals are required **prior** to the amendment being submitted to REC and HRA (and MHRA where appropriate). A procedure must be in place to ensure that the sponsor is given the opportunity to review each amendment, and it must detail the process for submission to appropriate regulatory bodies.

[3] http://ec.europa.eu/health/documents/eudralex/vol-10_en

5.9 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 and may then be delegated to the CTU managing the trial.

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.

5.10 Urgent Safety Measures

An Urgent Safety Measure is an action that the 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 the formal process of notification of the measure to the University as sponsor. Once the measure has been implemented a substantial amendment must then be made detailing the measure.

5.11 Annual Reporting to REC & MHRA

REC and MHRA require that annual reports and annual safety reports (Development Update Safety Reports [DSURs]) are submitted annually from the date of initial approval for the trial duration. The responsibility for the submission of these is delegated to the CI but may be undertaken by the CTU or another member of the study team to whom this task is further delegated. Guidance for the submission of these is available from REC and MHRA respectively and a procedure must be in place that details the submission.

5.12 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.

5.13 Archiving

The Clinical Trials Regulations and specifically, Regulation 31A of the Medicines for Human Use (Clinical Trials) Amendment Regulations 2006, define the archiving requirements for Clinical Trials of Investigational Medicinal Products (CTIMPs). All essential documents should be archived and this includes essential documents held by investigators, sponsors and others involved in the conduct of a clinical trial (including services departments such as pharmacy, laboratories and radiology).

Essential documents of the sponsor/trial organisers and investigators, from trials that are not to be used in regulatory submissions, should be retained for at least five years after completion of the trial. These documents should be retained for a longer period if required by the applicable regulatory requirement(s), the sponsor or the funder of the trial.

Consideration should be given for the archive of both paper and electronic data (such as databases). EMA Guideline on the content, management and archiving of the clinical trial master file (paper and/or electronic)' (December 2018) should be considered when developing systems for archive. This document includes guidance relating to the media used for storage of documents (including requirements when original records are transferred to electronic media for the purpose of archive). The CTIMP protocol may require that documents are retained for a longer period of time, or the CTU may also define a longer retention period. The University holds a contract with RESTORE Document Management Services which is available for the archiving of CTIMP documents.

6. Glossary of Terms

Term	**Definition**
Chief Investigator (CI)	Under the Regulations means – a) in relation to a clinical trial conducted at a single trial site, the investigator for that site; b) or in relation to a clinical trial conducted at more than one trial site, the authorised health care professional, whether or not he is an investigator at any particular site, who takes primary responsibility for the conduct of the trial
Clinical Trial of an Investigational Medicinal Product (CTIMP)	Any investigation in human subjects, other than a non-interventional trial, intended: a) to discover or verify the clinical, pharmacological or other pharmacodynamic effects of one or more medicinal products; b) to identify any adverse reactions to one or more such products; c) or to study absorption, distribution, metabolism and excretion of one or more such products; with the objective of ascertaining the safety or efficacy of those products.
Co-Sponsorship	A sponsorship arrangement whereby two or more organisations agree to act as sponsors, allocating responsibility between them for carrying out the functions of the sponsor.
CTA	Clinical Trial Authorisation
CTOC	Clinical Trials Oversight Committee

Term	Definition
CTU	Clinical Trials Unit
Clinical Trials Regulation (Regulation (EU) No 536/2014)	The Clinical Trials Regulation harmonises the processes for assessment and supervision of clinical trials throughout the EU. The evaluation, authorisation and supervision of clinical trials are the responsibilities of EU Member States and European Economic Area (EEA) countries.
HRA	Health Research Authority
ICH GCP	The International Convention on Harmonisation of Good Clinical Practice
Investigational Medicinal Product (IMP)	A pharmaceutical form of an active substance or placebo being tested, or to be tested, or used, or to be used, as a reference in a clinical trial, and includes a medicinal product which has a marketing authorisation but is, for the purposes of the trial: a) used or assembled (formulated or packaged) in a way different from the form of the product authorised under the authorisation, b) used for an indication not included in the summary of product characteristics under the authorisation for that product, or c) used to gain further information about the form of that product as authorised under the authorisation.
MHRA	Medicines and Healthcare products Regulatory Agency
REC	Research Ethics Committee
Principal Investigator (PI)	The clinician responsible for a team of investigators conducting a study at a particular site.
The Regulations	The Medicines for Human Use (Clinical Trials) Regulations 2004 (Statutory Instrument 2004 No. 1031)
Sponsor	The sponsor in this context is the body which guarantees or oversees the research. The Regulations define the sponsor as “an individual, company, institution or organisation, which takes responsibility for the initiation, management and/or financing of a clinical trial.
The University	The University of Liverpool

7. References

Regulation (EU) No 536/2014 of the European Parliament and of the Council of 16 April 2014 on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC https://www.legislation.gov.uk/eur/2014/536/contents

Medicines for Human Use (Clinical Trials) Regulations 2004 - http://www.legislation.gov.uk/uksi/2004/1031/contents/made

ICH Guideline for Good Clinical Practice Current *Step 4* version dated 10 June 1996 - http://ec.europa.eu/health/documents/eudralex/vol-10_en

MHRA/ DH/MRC Joint Project "Risk-adapted Approaches to the Management of Clinical Trials of Investigational Medicinal Products - http://webarchive.nationalarchives.gov.uk/20141205150130/http:/www.mhra.gov.uk/home/groups/l-ctu/documents/websiteresources/con111784.pdf

DAMOCLES Study Group. 2005. A proposed charter for clinical trial data monitoring committees: helping them to do their job well. *The Lancet* 365(9460), pp711–722

POL001 - Statement of Policy Sponsorship of Research

SOP004 - Sponsorship Application and Approval process