Clinical Directorate Clinical Research Governance Team

Standard Operating Procedure

Sponsor Audit

SOP025

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Approved on behalf of ratifying committee	**Date of Approval**
Professor Tom Walley (Chair of Clinical Research Regulatory Oversight Committee)	26th September 2024

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1. Introduction

Audit is used to evaluate the level of compliance of an organisation with defined standards. The primary purpose is to identify areas for corrective and preventative action (CAPA) for continual quality improvement of systems and processes. Audit is a planned and systematic independent activity and may focus on a specific function, process, quality system or a specific clinical trial.

The audit standards may be defined by organisational policies and procedures or by regulations or guidelines, including criteria set forth in the UK Medicines for Human Use (Clinical Trials) Regulations (2004) or the principles of Good Clinical Practice (GCP). Regulatory bodies, including the Medicines for Healthcare products Regulatory Agency (MHRA), expect organisations undertaking clinical research to have an established internal audit system as part of its Quality Assurance system.

2. Scope of Procedure

This SOP describes the process for production and management of the Sponsor Team Audit Programme, which includes the internal audit of University Sponsored Clinical Trials of Investigational Medicinal Product (CTIMP) and Clinical Investigations of Medical Devices (CIMD).

3. Who

This SOP is aimed at staff within the University Clinical Directorate who are involved in the auditing process for University Sponsored research.

This SOP is aimed at Chief Investigators, students, trial coordinators and other members of University Staff involved in University Sponsored research.

4. When

The Sponsor Audit Programme will be produced annually by the Sponsorship Manager or Senior Sponsorship Officer, and will include the following areas of audit:

- Oversight of University Sponsored CTIMPs and CIMDs;
- Clinical Directorate, Clinical Research Governance Procedures;
- Vendor approval of external CTUs undertaking management of University Sponsored CTIMPs and CIMDs.

The frequency and scope of the audits in each area will be identified based on a number of considerations, including recent regulatory inspections/reports; level of risk associated with the activity, evidence of potential or actual quality incidents and/or safety issues, evidence of other existing external scrutiny. Appendix 1 provides further information on the algorithm that will be used to assess the need for Sponsor audits.

The Audit Programme is to be ratified by the Clinical Research Regulatory Oversight Committee (CRROC) and will be presented at committee meetings through the year as part of ongoing University oversight. See SOP029 for more details of University Oversight processes.

The ratified Audit Programme may be amended within the annual period. The amended Audit Programme will be presented to and ratified by CRROC.

A maximum of 12 audits will be planned per annum from the above categories, however it is noted that triggered audits may be required where potential serious issues and/or integrity matters are identified with a study. It is also noted that vendor approval audits will be required when new, external CTUs are contracted with. The audit plan will be amended in line with triggered audits to ensure appropriate management of workload. Any changes to priority of audits will be discussed with the Senior Clinical Research Governance Manager and/or the Chair of CRROC to ensure that delay of a planned audit is appropriate.

5. Audit team

The Sponsorship Manager and Senior Sponsorship Officer will be primarily responsible for conducting audits but may identify that additional specialist support is required and will work with the Senior Clinical Research Governance Manager to ensure that there is the appropriate team in place to conduct the audit. The Lead Auditor will be identified and agreed prior to any correspondence with the auditees. This will be recorded in the audit record within Ideagen Quality Management, along with any additional Auditors.

Where an audit is of a Co-sponsored CTIMP the Lead Auditor will notify the Co-Sponsor of the intention to audit. It is generally expected that the Co-Sponsor will provide an auditor to undertake the audit along with the University, however where arrangements are in place it may be agreed that one Co-Sponsor will undertake the audit of the study and provide the report to the other. This is to avoid duplication of effort on behalf of the Co-Sponsors and the auditee department. If the Co-Sponsor does not wish to undertake the audit the Lead Auditor will only audit the functions related to the University responsibilities detailed in the Co-Sponsorship agreement.

6. Audit schedule

Audits of University departments external to the Clinical Research Governance Team and external organisations will follow the below schedule of events which will be agreed with the auditees prior to the audit being carried out;

Timing	Item	Purpose
30 working days prior to the scheduled audit	Initial contact	The Lead Auditor will contact the department to be audited to identify the contact person for the audit and agree the date for audit. The Lead Auditor may at this stage ask for documentation such as SOPs or organisational charts to assist in the planning of the audit
10 working days prior to the audit	Confirmation of audit and draft audit plan	The Lead Auditor will confirm with the auditees the date and location of the audit, the documentation that will be reviewed and

Timing	Item	Purpose
		the personnel to be interviewed. An audit plan will be provided for review (TEM003).
3 working days prior to audit	Audit plan	The Lead Auditor will provide the finalised audit plan to the auditees
On audit day	Opening meeting	To discuss the scope of the audit, to define the reporting process and to receive any documentation not received beforehand (i.e. confidential documents)
On audit day	Audit	The audit will be carried out using reference documentation and interviews with personnel if required. The auditor(s) will attempt to resolve all queries prior to the closing meeting
On audit day	Closing meeting	The Lead Auditor will report their findings to the auditees and ensure understanding of the findings and conclusions and the reporting and follow up procedures. This meeting will inform the final report.
20 working days after the audit	Final Report	The final report (TEM002) will be submitted to the auditees which will contain the findings and conclusions, and if appropriate recommendations.

Internal audits may also follow the same schedule depending on the audit being conducted. For audits of sponsorship processes the Sponsorship Officers will work with the Lead Auditor to conduct the audit by providing lists of studies where appropriate.

7. Preparation for Audit

Prior to the audit the Lead Auditor will work with the relevant team to identify a contact person for the audit process to confirm a date and time for the audit.

The Lead Auditor will also produce an audit plan detailing the scope and proposed schedule of audit activities. A draft will be sent to the auditees at least 10 working days before the audit and the finalised copy will be sent to the auditees no later than 3 working days prior to the audit start date.

During the audit preparation process the Lead Auditor will assess where the audit is to be carried out, either on location or virtually. Where assessment of source data is required (such as a Trial Master File) then it will be preferred that an on-site audit be undertaken.

8. Audit Conduct

Various audit techniques may be used to determine the effectiveness of the area being audited, including interviewing of staff involved in the management of the process and a review of documents/records. The Lead Auditor will determine the appropriate methods for auditing the process specified and will produce an audit checklist which will form the basis of the audit criteria.

The Lead Auditor will compile and discuss observations with the primary contact during the auditing process to try and come to a resolution. Any unresolved findings will be discussed at the closing meeting and included in the final report.

Findings will be graded according to the following criteria:

Critical	Where evidence exists that significant and unjustified departure(s) from applicable legislative requirements has occurred with evidence that: • the safety or well-being of trial subjects either have been or have significant potential to be jeopardised, and/or • the clinical trial data are unreliable and/or • there are a number of Major non-compliances across areas of responsibility, indicating a systematic quality assurance failure, and/or • Where inappropriate, insufficient or untimely corrective action has taken place regarding previously reported Major non-compliances
Major	A non-critical finding where evidence exists that a significant and unjustified departure from applicable legislative requirements has occurred that may not have developed into a critical issue, but may have the potential to do so unless addressed, *and/or* Where evidence exists that a number of departures from applicable legislative requirements and/or established GCP guidelines have occurred within a single area of responsibility, indicating a systematic quality assurance failure.
Minor	All other findings.
Recommendations, considerations and opportunities for improvement	Areas that are not considered a formal finding but provide feedback and opportunities for improvement to help prevent formal findings at a future audit or inspection.

9. Audit reports

The Lead Auditor will escalate any critical risks identified during the audit to the Senior Clinical Research Governance Manager and Chair of CRROC in a timely manner and before distribution of the audit report.

A finalised audit report will be completed within 20 working days from audit completion.

The final audit report will be provided to the primary contact for response and further dissemination.

The Lead Auditor will maintain original copies of all audit reports.

10. Response to audits

Written responses and identified CAPAs are to be submitted by the primary contact within 20 working days from the distribution of the approved audit report.

The Lead Auditor will assess the acceptability of the response.

Depending upon the severity/risk associated with the finding the Sponsorship Manager may request to verify the effectiveness of the CAPA prior to accepting the response.

A copy of the approved audit report, audit materials and responses will be retained by the Lead Auditor for any regulatory inspections or internal monitoring purposes.

The primary contact is responsible for implementing and maintaining any CAPAs identified from the approved audit report and within the specified timelines. Progress should be reported to the Lead Auditor who will request a quarterly update on this until all actions are completed.

The CAPA will be added to the audit record in Ideagen Quality Management system and progress will be tracked by the Lead Auditor until all actions are completed.

Following acceptance of suitable responses and upon completion of verification (if required) the Lead Auditor will close out the audit and notify those involved.

The Senior Clinical Research Governance Manager will collate and provide a summary of conducted audits to the CRROC.

11. Vendor Selection

The Sponsor will undertake a Vendor Selection Audit whenever a new, external CTU are contracted with for a CTIMP. These audits will be repeated after 3 years, or earlier if substantial change has occurred within the CTU.

The Sponsor does not undertake routine Vendor Selection Audits for vendors other than a CTU, but where a vendor is undertaking a key role in a trial the Sponsor will utilise FORM017 External Vendor Questionnaire to assess the suitability of the vendor and determine if an audit may be required.

If a CTU or other organisation undertaking trial management functions for a University Sponsored CTIMP plan to use an electronic Trial Master File (eTMF) then FORM018 Electronic Trial Master File requirement check list must be completed.

All laboratories selected to undertake any activity for a CTIMP will be required to complete FORM013 GCP Laboratory Self-Assessment Questionnaire to assess their suitability. FORM013 for each laboratory must be reviewed and signed by the Sponsor before the trial can open to recruitment, as part of the Permission to Proceed process.

12. Roles and Responsibilities

Sponsorship Manager/Senior Sponsorship Officer

- Develop audit schedule

Lead Auditor

- Conduct audits
- Discuss findings with relevant personnel as described above
- Produce audit reports and distribute as necessary
- Escalate any critical findings to the Senior Clinical Research Governance Manager and Chair of CRROC
- Verify responses to audit findings (if necessary)
- Accept responses to audit findings
- Maintain records of audit, findings and CAPA in Ideagen Quality Management system
- Receive progress report against CAPA as required

Senior Clinical Research Governance Manager

- Review critical findings and advise on any required escalation/action required
- Develop audit tools, as required
- Review and update of Audit SOP as required
- Provide summary of conducted audits to the CRROC

Chair of CRROC

- Review critical findings and advise on any required escalation/action required

CRROC

- Review summary of conducted audits and review progress of CAPA completion
- Ratify annual audit plan and updates to this

Chief investigator/Department Head of Activity Area/Auditee

- Facilitate audit procedure
- Ensure that agreed CAPA are implemented and actioned within pre-agreed timelines and provide progress updates on a quarterly basis

13. Abbreviations

CI Chief Investigator

CAPA Corrective and Preventative Actions

CIMD Clinical Investigations of Medical Devices

CRROC Clinical Research Regulatory Oversight Committee

CTIMP Clinical Trials of Investigational Medicinal Product

GCP Good Clinical Practice

MHRA Medicines for Healthcare products Regulatory Agency

LHP Liverpool Health Partners

14. Associated Documents and References

TEM002	Audit Report Template
TEM003	Audit Plan template
SOP011	Monitoring of University Sponsored CTIMPs
SOP029	Organisational Oversight of CTIMPs
FORM013	GCP Laboratory Self-Assessment Questionnaire
FORM017	External Vendor Questionnaire
FORM018	Electronic Trial Master File requirement checklist

The Medicines for Human Use (Clinical Trials) Regulations 2004 (SI 2004 No. 1031)

The Medical Devices Regulations 2002

15. Training and Resources

Clinical Directorate staff who are involved in the auditing process for University Sponsored research should fully read and understand this SOP. CIs, trial coordinators and other members of University Staff involved in University Sponsored research should be aware of and familiar with this SOP. Training can be provided by the Clinical Research Governance Team upon request.

16. Monitoring and Audit

An internal audit of Clinical Directorate SOPs will be conducted at a minimum of every two years.

17. Appendix 1 – University of Liverpool Sponsor Audit Algorithm

The Sponsorship Manager/Senior Sponsorship Officer will maintain an audit planner that will detail all University Sponsored CTIMPs and CIMDs which will be used to plan the annual audit plan.

When a newly Sponsored CTIMP or CIMD is approved for Sponsorship an assessment of the inherent study specific risk red flags will be made as detailed below.

All early phase trials (I & II) will automatically be red-flagged and should be subject to an audit as soon as possible after the trial opens to recruitment.

For CIMDs early phase (I & II) non-CE-Marked device investigations will be automatically red flagged and should be subject to an audit as soon as possible after the trial opens to recruitment.

Other red flags are detailed below and the inclusion of any of these will automatically raise the risk rating.

Trials will be subject to audit once recruitment has started, and dependent on the duration of the trial, the below will be adhered to Trials with an inherent high-risk rating should be audited on a minimum of once every 2 years;

- Trials with an inherent medium risk rating should be audited on a minimum of once every 3 years;
- Trials with an inherent low risk rating should be audited at least once during the duration of the trial.

Inherent Study-specific risk "red-flags"
External or no CTU
International site(s)
Vulnerable participants; • Children under the age of 5 • Pregnant Women • Participants without the capacity to consent

CTIMPs	Phase			
Type	I	II	III	IV
C	**HIGH**	**HIGH**	**HIGH**	**MEDIUM**
B	**HIGH**	**HIGH**	**MEDIUM**	**MEDIUM**
A	**HIGH**	**HIGH**	**MEDIUM**	**LOW**

CIMDs	Phase			
Type	I	II	III	IV
Non CE-Marked	**HIGH**	**HIGH**	**MEDIUM**	**MEDIUM**
CE-Marked	**HIGH**	**MEDIUM**	**MEDIUM**	**LOW**

As trials progress it is noted that there may be ongoing non-compliances that will constitute a red flag being raised. Once a trial has reached 5 of the below the risk will be automatically raised to high and will be audited as soon as practicable.

Minor Non-Compliance "Red flags"
Potential serious breach
Major audit/inspection findings
Data protection breach

If any of the following occur on a single occasion the risk will be automatically raised to high and will be audited as soon as practicable.

Non-Compliance automatic "Red flags"
Actual serious breach
Critical audit/inspection findings
Critical trial events (i.e. unexpected participant death)
Sudden and unexplained increase in Serious Adverse Events