UNIVERSITY OF LINCOLN

CLINICAL GOVERNANCE STANDARD OPERATING PROCEDURE

Monitoring and Audit

CG-QMS SOP CG13

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Version History	**Reason for change**

NOTE: All SOPs are subject to regular review.

Please ensure that the version of this SOP is the most up-to-date.

OUT OF DATE DOCUMENTS MUST NOT BE USED AND HARD COPIES SHOULD BE DESTROYED

1. PURPOSE

To ensure that the Researchers, Lincoln Clinical Trial Unit (LinCTU) and Research Governance Team (RGT) members understand the requirement and procedures for the audit and monitoring of procedures associated with clinical research.

To provide clear instructions to the authorised staff from LinCTU and RGT for the internal audit of clinical research conducted by or managed by University of Lincoln.

2. SCOPE

Applicable to all researchers undertaking clinical research. As well as members of the RGT who are responsible for carrying out audits and monitoring under direction of the Sponsor.

3. BACKGROUND

3.1 This Standard Operating Procedure (SOP) forms part of the University's Clinical Governance Quality Management System (HCG-QMS) for the governance of clinical research.

3.2 Clinical research is defined as research that falls within the remit of the UK Policy Framework for Health and Social Care Research.

3.3 Clinical research may also include Clinical Trials of Investigational Medicinal Products (CTIMPs) as governed by the UK Clinical Trials Regulations.

3.4 Monitoring is an integral process in the Quality Control (QC) of a trial. Monitoring ensures that a trial it is conducted, recorded, and reported in accordance with the trial protocol, applicable SOPs, policies, GCP, and the applicable regulatory requirement(s) (section 1.38 ICH Guideline for Good Clinical Practice E6 (R2), dated 9 November 2016.)

3.5 According to the principles of ICH GCP (section 5.18.1, ICH Guideline for Good Clinical Practice E6 (R2), dated 9 November 2016.) the purposes of trial monitoring is to verify that:

- *The rights and well–being of human subjects are protected.*
- *The reported trial data are accurate, complete and verifiable from source documents.*
- *The conduct of the trial is in compliance with the currently approved protocol/amendment(s), with GCP, and with the applicable regulatory requirement(s).*

3.6 The audit process is defined by the International Conference on Harmonisation (ICH) (section 1.6) Good Clinical Practice (GCP) guidelines as:

> *'A systematic and independent examination of trial-related activities and documents to determine whether the evaluated trial related activities were conducted, and the data were recorded, analysed and* accurately reported according to the protocol, sponsors SOPs, GCP and the applicable regulatory requirements'.

3.7 An Auditee is defined as; a person or organisation that is audited

3.8 Sponsor organisations (institutions that take responsibility for initiation, management and/or financing of a clinical trial), are legally responsible for auditing research practice and assuring adherence to current legislation and guidelines.

3.9 The Research Governance Manager (RGM) on behalf of the Sponsor is responsible for devising an audit schedule of clinical research. Once devised the audit schedule shall be approved by the Sponsor.

3.10 Corrective and Preventative Action(s) (CAPA) are improvements to processes taken to eliminate causes of non-conformities or other undesirable situations. It is usually a set of actions which are required to be taken and implemented in an organization at levels of manufacturing, documentation, procedures or systems in order to rectify and eliminate the recurrence of nonperformance.[1]

[1] https://en.wikipedia.org/wiki/Corrective_and_preventive_action

3.11 Monitoring/Audit reports and CAPA plans may be presented to the Sponsor. The Research Governance Manager will report to University Research Ethics Committee (UREC) in accordance with E-QMS SOP E-01 Ethics Committee: Operations (Committee Structure & Terms of Reference).

3.12 Internal audits may also be conducted in conjunction with the University of Lincoln Human Tissue Oversight Group, where clinical research also involves the acquisition, storage, use and disposal of human samples for research stored at the University of Lincoln.

3.13 Externally sponsored trials will be audited in line with the requirements detailed in the collaboration agreement or division of responsibilities document.

4. CROSS REFERENCES

4.1 CG-QMS RF CG13-RF01 Audit Report

4.2 CG-QMS RF CG13-RF02 CAPA Plan

4.3 CG-QMS RF CG13-RF03 CAPA Log

4.4 CG-QMS SOP CG01 Training

4.5 CG-QMS SOP CG10 Adverse Events

4.6 E-QMS SOP E-01 Ethics Committee: Operations (Committee Structure & Terms of Reference)

4.7 HT-QMS: All SOPs, Record Forms and Work Instructions

4.8 RG-QMS RG01 Design and Review of Standard Operating Procedures

4.9 RG-QMS RG02 Document Control – (QMS documents)

4.10 RG-QMS RG03 Document Control – (Study documents)

4.11 UK Clinical Trials Regulations

4.12 https://www.hra.nhs.uk/planning-and-improving-research/policies-standards-legislation/uk-policy-framework-health-social-care-research/uk-policy-framework-health-and-social-care-research/

5. PROCEDURE

Routine Monitoring

5.1 Monitoring visits shall be arranged locally (as required) by the CI, Principal Investigator (PI) or relevant LinCTU member.

5.2 Monitoring visits allow for informal discussions with researchers in the working environment, to obtain feedback on SOPs, any changes in related local procedures, additional training needs and any additional resources that are required.

5.3 Monitoring visits shall be conducted in accordance with the clinical trial protocol and shall involve a number of activities to ensure that sites remain fit for purpose or highlight areas for adjustment or improvement when supporting clinical research:

5.4 Informal discussion with researchers relating to SOPs, local procedures and any training needs identified

5.5 A review of trial-specific essential documents or system documentation (e.g. computer system validation package, protocols)

5.6 Participant Records including Source Data Verification

5.7 Note: Routine Monitoring shall compliment other health and safety monitoring and the principles of Good Clinical Practice (GCP) where applicable.

5.8 Monitoring shall also involve:

- Informal review of training (in accordance with SOP CG01 Training
- Logging and investigation of adverse events and incidents (in accordance with SOP CG10 Adverse Events)

5.9 Informal Monitoring reports shall be made available to the sponsor as required, a copy should be retained in the Trial Master/Investigator site file.

5.10 Routine (Regular) Audit

5.11 The RGM on behalf of the Sponsor shall devise a routine audit schedule to review activities relating to the conduct of clinical research and to provide evidence of compliance with Clinical Trial Authorisations (where relevant). Once devised the audit schedule shall be approved by the Sponsor.

5.12 Routine audits shall be carried out by the RGM and/or delegated LinCTU member(s) (auditor(s)) and shall identify appropriate staff(s) to accompany in order to undertake the audit. Researchers (auditees) shall be notified in advance (via email) of the impending audit and shall arrange a suitable date and time. The auditee is responsible for arranging a suitable venue for audit to take place (such as office space/meeting room).

5.13 Objectives of routine audits are to:

- Ensure participants rights and welfare are being adequately protected
- Assist researchers with compliance to regulatory requirements and University policy
- Assure regulatory compliance
- To assess whether staff working on the trial are appropriately trained, are clear of their role and are working to GCP, the protocol and standard operating procedures (SOPs)
- Prepare researchers for potential future external regulatory inspections
- Aid in identifying and correcting problem areas and provide suggestions to improve quality.

5.14 The auditor(s) shall draw up a checklist for the audit identifying human tissue samples and documents to be examined and shall consult with relevant SOPs and review previous audit reports and CAPAs (where appropriate).

5.15 Audits will cover the full range of clinical research conducted by the University of Lincoln (and not limited to):

- Trial Master File/Document audits: A review of trial-specific essential documents or system documentation (e.g. computer system validation package, protocols)
- System audits: Looking at the functionality of complete systems (e.g. pharmacovigilance, data management)
- Process audits: looking at the performance of a specific processes within systems (e.g. expectedness assessments, data query process)
- Vendor audits: assessment of external service providers (e.g. clinical trial drug supply companies, courier service

5.16 Records relating to the conduct of clinical research shall be scrutinised (including but not limited to):

- Facilities
- Staff training
- Essential documentation in accordance with CG-QMS CG07 Trial Master / Site File
- Consent forms and process
- Safety reporting procedures
- Drug storage and accountability (if applicable)
- Reviews of study conduct and processes
- Risk assessments
- Participant records/Case Report Forms

Note: Participant Records shall be selected at random by the auditor.

5.17 Routine audits shall be conducted with the support of Lead Researcher and any other researchers/technical staff as appropriate.

5.18 The auditor(s) shall review the implementation of the CG-QMS and relevant CGSOPs and the effectiveness of the system.

5.19 Where an audit has been conducted previously, the auditor(s) shall assess the implementation of any corrective and preventative action plans (CAPA) which had previously been identified.

5.20 At the time of the audit, an audit report shall be compiled using RF CG13-RF01 Audit Report, good practice shall be highlighted, any non-conformities and responses identified shall also be reported.

5.21 Audit findings will be graded using the following criteria:

Major: a finding defined as one with the capacity to put participants at immediate risk or directly undermine the integrity of the entire trial. For example:

- Where evidence exists that the safety, wellbeing, rights or confidentiality of trial participants has been (or has significant potential to be) jeopardised.
- Where approval of the trial has not been sought or granted from one or more regulatory body (e.g. Ethics committee, MHRA) but the trial has commenced regardless.
- Where procedures not included on the consent form are being performed or new procedures have been introduced but participants have not been asked to re-consent.
- Where significant amendments have been made to the protocol but no new request for approval has been submitted.
- Critical checks on data relating to safety and compliance are not being carried out
- Failure to take appropriate steps to protect personal data
- Where reason has been found to cast serious doubt upon the accuracy and/or credibility of trial data.

Moderate: a finding defined as one that compromises the integrity of a certain component (or components) of the trial. For example:

- Where there has been a significant and unjustified departure from UK regulations or GCP guidelines e.g. failure to provide participants with a copy of their consent form or Participant Information Sheet (PIS).
- Where there have been a number of minor departures from the UK regulations or GCP, suggesting a systematic quality assurance failure.

Minor: any other audit findings defined as those where the integrity of the trial is not directly compromised but which represent a lack of due diligence on behalf of trial staff towards the conduct of the trial. For example:

- Findings which demonstrate that no definite document management systems are in place at site.
- Where there has been a failure by trial staff to inform the relevant authorities of amendments to start/stop dates or study specific documents.
- Poor version control
- Data Management Plan does not reflect actual processes

5.22 Following completion of the audit (and within 5 working days), the auditor(s) shall discuss with the auditee (Individual Responsible) and any other relevant persons the findings of the audit. Non-conformities found shall be discussed and a CAPA plan drawn up using RF CG13-RF02 CAPA Plan.

5.23 CAPA Plans are uniquely referenced using an identifier in the following format yy/mm/letter(s) and logged using CG-QMS CG02-RF03 CAPA Log (held in RGM office).

5.24 The CAPA plan shall be formally agreed, with target dates for CAPA to be implemented. Both the auditor(s) and the auditee shall sign the CAPA plan.

5.25 The auditee shall address and implement CAPA in light of the CAPA plan within the agreed timeframe. The auditee shall return completed CAPA plan to HTOG/RGM for review and sign off.

5.26 A copy of the completed and fully signed CAPA plan (RF CG13-RF02 CAPA Plan) and Audit Report (RF CG13-RF01 Audit Report) shall be filed both in the Study Master File and electronically in the Routine Audit File (stored in the RGM office).

5.27 The CAPA plan (HT-QMS HT02-RF02 CAPA Plan), Audit report (RF CG13-RF01 Audit Report) and CAPA Log (CG-QMS RF CG13-RF03 CAPA Log) shall also be made available at the next UREC meeting.

5.28 If any findings potentially constitute a serious breach, actions should be taken in line with CG-QMS CG11 Serious Breach'.

Ad Hoc/Triggered Audit

5.1 The Research Governance Manager or authorised LinCTU staff may conduct unscheduled and unannounced audits (spot-checks) as a result of an adverse event or incident, or in an area where poor practice may be suspected.

5.2 If any findings potentially constitute a serious breach, actions should be taken in line with CG11 Serious Breach'.

Amendments to CG-SOPs

5.3 An audit may identify areas of inadequacies/discrepancy in the CG-QMS. Where inadequacies/discrepancies are identified, the RGM shall initiate and implement any changes to the CG-QMS in accordance with RG-QMS RG01 Production, Review, Approval, Distribution, Revision and RG-QMS RG02 Document Control and discuss as appropriate.

External Audit and HTA Inspection

5.4 Audits may be conducted by external agencies including site inspections by the MHRA. Members of the Research Governance Team shall support the auditor(s) in their duty.

5.5 Any reports and CAPA arising from such inspections shall be considered by the Research Governance Manager with recommendations agreed by the Sponsor for any significant changes in the HCG-QMS. Changes to CG-QMS will be in accordance with RG-QMS RG01 Design and Review of Standard Operating Procedures.

5.6 A copy of the audit report and any CAPA arising shall also be presented to UREC (with escalation as required).

6. DEFINITIONS

A full list of definitions may be found in the Clinical Governance Quality Manual (CG-QM) available at https://lncn.ac/clinicalSOPs

7. Flow Chart

Routine (Regular) Audit