Standard Operating Procedure R&D/SOP002

Quality Assurance Audits

1. Scope

The audit of EU Clinical Trials of Investigational Medicinal Products (CTIMPs) sponsored by the Trust and the audit of the Trust's quality management systems

2. Purpose

Good Clinical Practice requires that Sponsors of EU clinical trials have in place Quality Assurance mechanisms to ensure that trials are conducted in accordance with GCP. This SOP describes the procedure for the audit of EU Clinical Trials of Investigational Medicinal Products (CTIMPs). This SOP does not preclude the Audit of non-CTIMPs which will be audited to national best practices.

3. Definitions and Abbreviations

The headings below contain the definitions of terms and meaning of abbreviations used within the document.

3.1. Definitions

Term	Definition
Cambridge Sponsored	Sponsored by Cambridge University Hospitals NHS Foundation Trust (CUH); or the University of Cambridge (UoC); or jointly by CUH and UoC or Cambridgeshire & Peterborough NHS Foundation Trust (CPFT) or CPFT jointly with the University of Cambridge
For cause	Where issues concerning a trial have been identified

3.2. Abbreviations

Abbreviation	Meaning
GCP	Good Clinical Practice
TMF	Trial Master File
CAPA	Corrective and Preventive Action
ReDA	Research Application Database(tool to capture trial details)

4. Undertaken by

Auditors and R&D staff. The R&D Manager may delegate another member of the R&D Clinical Trials team to conduct the R&D Manager's activities.

5. Items Required

Quality File

Access to Source Data:

- Trial Master Files
- Training Records
- Standard Operating Procedures
- R&D File
- Misconduct and Fraud –Good research Practice ID12622 http://www.cuh.org.uk/research-and-development/document-library

6. Summary of Significant Changes

Minor corrections and clarifications from the previous version.

7. Method

The following sections provide a description of the processes to be followed when implementing this document's procedures.

7.1. Quality File

- The R&D Manager maintains a Quality File in which the following documents are held:
    - CV of auditor(s)
    - Confidential Disclosure Agreement (CDA) with auditor(s)
    - Auditor contract(s) including an outline of responsibilities
    - Annual Quality Assurance Audit Strategy
- For individual audits:
    - Audit Plan
    - Audit Schedule
    - Audit Report
    - Corrective and Preventative Action Plan
    - Associated significant correspondence
    - Copies of audit certificates
- Documents in the Quality File relating to individual audits are made available for inspection on request
- Note: Original audit certificates are held in the TMF.

7.2. Auditors

- The R&D Manager is responsible for ensuring that a suitably qualified auditor is appointed
- The CV of the auditor is filed in the Quality File, and should include evidence of recent GCP training (within previous 2 years)
- The scope of the auditor's activities should be detailed in their contract

7.3. Internal Audits

- Audits of the Sponsors quality management systems will be undertaken as required by the R&D Manager
- The purpose of these audits will be to confirm that the Sponsor's SOPs are being followed and that GCP compliance is being maintained
- A formal audit schedule should be documented and any deviations from this should be noted

7.4. Audit of Clinical Trials

- QA audits of CTIMPs are undertaken to ensure that clinical trials are conducted according to relevant EU and UK Clinical Trial legislation, GCP, The Department of Health Research Governance Framework for Health and Social Care and any internal Research Governance Procedures
- An annual Quality Assurance Audit Strategy may be prepared which will outline the number of trials to be audited during the year and specific selection criteria to be employed
- In addition, it may be necessary to conduct a specific "for cause" audit where compliance issues have been identified
- Each year approximately 10% of trials are subject to routine audit by an independent QA auditor
- The selection of trials to be audited is based on the size, type and complexity of the study and other risk assessment factors identified by the Sponsor during the conduct of the study and/or during monitoring
- The R&D Department supplies the auditor with a list of current trials from which the auditor makes an independent selection
- The R&D Manager ensures that the relevant notification form is completed and submitted to the Clinical Audit Department
- The R&D Manager or designee informs the Chief/ Principal Investigator by letter if their trial has been selected for audit
- At least 4 weeks notice of an audit should be given to the Investigator unless the audit is "for cause"
- The R&D Department and/or the auditor liaises with the investigator and agree a date for the audit
- The auditor forwards any further information to the investigator including the audit plan and schedule

7.5. Audit Plan

- The audit plan clearly sets out the objectives of the audit:
  - The standards to be applied (applicable legislation and SOPs),
  - The activities to be included in the audit (documents and facilities to be reviewed, interviews etc)
  - The reporting mechanisms and subsequent follow-up
- The draft audit plan is submitted to the R&D Manager (and the investigator for clinical trial audits) for comment, and then finalised
- The final audit plan also includes a schedule

7.6. Audit Schedule

- The timings of the audit activities
- The time and place for the introductory meeting to which all relevant staff are invited
- The time and place of the exit meeting at which the auditor gives verbal feedback on the findings of the audit and at which any outstanding issues can be clarified

7.7. Conduct of the Audit

- The auditor conducts the audit as outlined in the audit plan
- For audits of an EU clinical trial
- The audit includes a review of:
    - The Trial Master File (TMF)
    - All informed consent forms
    - A selection of Case Report Forms and associated source data
    - Training records
    - Departmental standard operating procedures, as applicable
    - A review of facilities where the research has taken place, including clinical areas, pharmacy and laboratories as appropriate
    - Other items may be added as required.

For audits of Sponsor quality management systems

- The audit includes a review of:
    - Documents and procedures outlining the Sponsor's responsibilities and activities
    - Compliance with the relevant legislation for the area
    - A review of records either paper or electronic which contain evidence for the conduct of the trial
    - Associated facilities and equipment
- For non-CTIMPs, the audit will be based on appropriate Sponsor documentation

7.8. Categories of Findings

- All findings identified during the audit are documented and categorised as follows:
    - CRITICAL – where non-compliance with Good Clinical Practice standards is affecting the integrity of the clinical trial or patient safety and corrective action is required immediately
    - MAJOR – where non-compliance with Good Clinical Practice standards has the potential to affect the clinical trial or patient safety if not corrected in a timely manner
    - OTHER – minor non-compliances with no significant impact on the outcome of the trial or patient safety

7.9. Reporting

- Audit Reports are filed in the Quality File

7.9.1. Preliminary Feedback

- The auditor makes immediate feedback (normally within 48 hours) by email, telephone or in person to the R&D Manager
- The feedback is an overview of any critical or major findings identified
- The auditor should send acknowledgement of thanks to the investigator where applicable
- The R&D Manager notifies the R&D Director immediately of any critical or major non-compliance identified

7.9.2. Initial Report

- The auditor prepares an initial report normally within 10 working days of the audit which is forwarded electronically to the R&D Manager
- Onward dissemination of the initial audit report is controlled by the R&D Manager

7.9.3. Clinical Trial Audit Report

- The report is forwarded to the investigator
- If the report contains any critical findings it is also forwarded to the R&D Director
- The R&D Manager or designee liaises with the investigator to coordinate a Corrective and Preventative Action (CAPA) Plan
- According to the critical findings, the Misconduct and Fraud policy and procedure may also be followed http://www.cuh.org.uk/research-and-development/document-library

7.9.4. Quality Management Systems Audit Report

- The report is forwarded to the R&D Director.
- The R&D Manager or designee coordinates the preparation of a CAPA Plan

7.9.5. Final report

- A final report, incorporating the CAPA Plan and any responses received from the R&D Manager and/or the investigator is prepared normally in twenty working days after the initial report
- The final signed hard copy report is sent to the R&D Manager who files it in the Quality File and controls any onward dissemination
- The ReDA database (or any other appropriate database) should be updated with the date of the audit and any subsequent reminders set

7.10. Audit Responses

- In the event of critical and/or major non-compliances identified action must be taken to resolve the non-compliance as soon as possible

7.10.1. Clinical Trial Audit Response

- The R&D Manager liaises with the investigator to agree responses to all findings
- outlined in the audit report
- Responses should include:
- Analysis of the cause of the finding
- Action to be taken to rectify the specific non-compliance (corrective action)
- Amendments to existing systems and procedures where necessary (preventative action)
- For each response the individual or group that will be responsible for carrying out the action should be identified
- A deadline should be agreed by which the action will be completed.
- The responses are compiled into a CAPA Plan which is signed by the investigator
- A copy is placed in the Quality File

7.10.2. Quality Management Systems Audit Response

- The R&D Manager liaises with the staff involved in the audit to agree responses to the findings in the audit report
- The CAPA Plan is forwarded to the auditor normally within 20 working days of the issue of the initial audit report for inclusion in the final audit report
- The final audit report, including the CAPA, is signed by the auditor, the investigator and the R&D Manager. A copy is placed in the Quality File

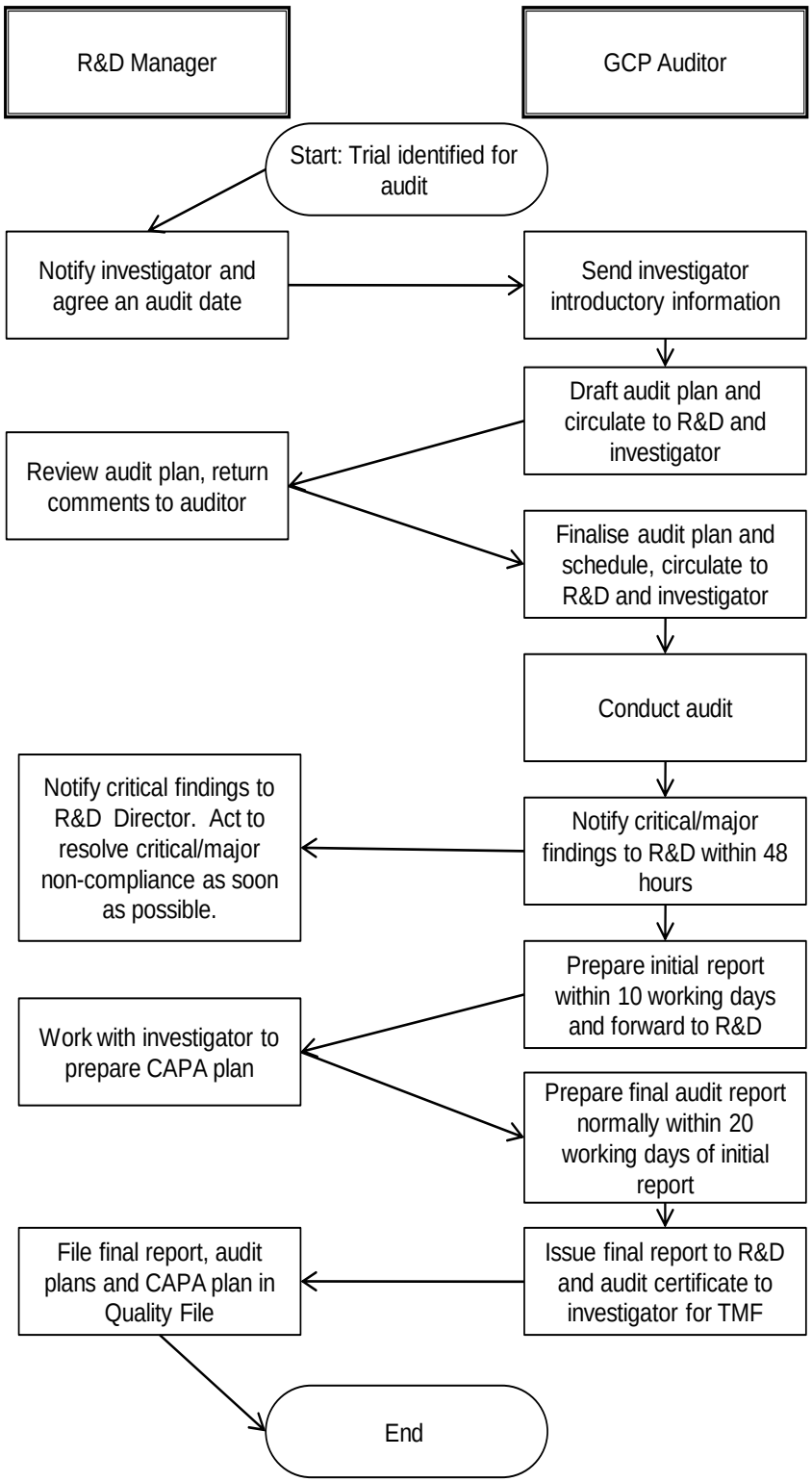
7.11. Audit Certificate

- Following the publication of the final audit report, an audit certificate is issued to the investigator for filing in the TMF
- The investigator and research staff are reminded by R&D Department staff that audit reports must not be filed in the TMF.

7.12. Audit Feedback

- A presentation of the audit findings by the Auditor will be given to the CI's and their trials teams on an annual basis.

Flow Chart for GCP Audit of an EU Clinical Trial of an Investigational Medicinal Product



8. Monitoring Compliance with and the Effectiveness of this Document

a. Process for Monitoring Compliance and Effectiveness

As part of routine monitoring visits, audit and inspection

b. Standards/Key Performance Indicators

This process forms part of a quality management system and is reviewed according to CCTU procedures. Standard Operating Procedures are reviewed every two years.

9. References

The Institute of Clinical Research, Abbreviations used in Clinical Trials.

MHRA, Good Clinical Practice "Grey Guide"

International Conference on Harmonisation (ICH) Guideline: E6 – Good Clinical Practice.

European Union Directives: 2001/20/EC, 2005/28/EC.

United Kingdom Statutory Instrument 2004/1031, Medicines for Human Use (Clinical Trials) Regulations and amendment regulations.

The Research Governance Framework for Health and Social Care, second edition 2005.

10. Associated Documents

None

11. Equality and Diversity Statement

This document complies with the Cambridge University Hospitals NHS Foundation Trust service equality and diversity statement.

12. Disclaimer

It is the user's responsibility to check against the electronic library that this printed out copy is the most recent issue of this document.

Review date	2 years (or earlier in light of new evidence) from approval date
Owning department:	CCTU QA
Supersedes:	R&D/SOP002 version 1
Local reference:	R&D/SOP002 version 2