Standard Operating Procedure CCTU/SOP011

Monitoring Cambridge Sponsored CTIMPs

1. Scope

It is the Sponsor's responsibility to ensure the trials are adequately monitored according to GCP. This SOP applies to monitoring activities for all Cambridge Sponsored CTIMPs.

2. Purpose

The purpose of monitoring of CTIMPs, as defined in ICH-GCP E6 (R2) and the MHRA Good Clinical Practice Guide is to verify that:

- The safety, rights and well-being of trial participants are protected
- Investigators are appropriately selected, trained and supported to complete the proposed clinical trial
- Processes are consistently followed and activities are consistently documented to ensure high quality trial conduct and protocol compliance
- The reported trial data is accurate, complete and verifiable against the 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)This SOP can be used to guide the trial team when they carry out site monitoring

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
Central Trial Team	Team responsible for the central conduct of the trial across all sits. Consists of Clinical Trial Coordinators, Data Managers, Programmers and Statisticians etc.
Quality Assurance	Planned and systemic actions that are established to ensure that the trial is performed and the data generated, documented (recorded), and reported in compliance with GCP and the applicable regulatory requirement.

Quality Control	Operational techniques and activities undertaken within the quality assurance system to verify that the requirements for quality of the trial-related activities have been fulfilled.
Monitoring	The act of overseeing the progress of a clinical trial, and of ensuring that it is conducted, recorded, and reported in accordance with the protocol and any amendments, SOPs, GCP
Departmental / External Monitor	Departmental / External Monitors are monitors contracted to carry out monitoring activities for a specific trial or department.
EPIC	Electronic Patient Record system used at CUH
TMF	Trial Master File encompassing the Main TMF, the Site Investigator File (SIF), the Statistics File, the Data Management File etc.

3.2. Abbreviations

Abbreviation	Meaning
CI	Chief Investigator
CTC	Clinical Trial Coordinator
CTIMPs	Clinical Trials of Investigational Medicinal Products
CTM	Clinical Trials Monitor
GCP	Good Clinical Practice
IMP(s)	Investigational Medicinal Product(s)
PI	Principal Investigator
SDV	Source Data Verification
SOP	Standard Operating Procedure
TMF	Trial Master File

4. Undertaken by

This SOP is applicable to all CCTU CTMs, CTCs, Trial Teams, Departmental Monitors, External Monitors (funded through trial budget for monitoring of specific trials) and Central Trial Teams as appropriate.

5. Items Required

This list of items required is not exhaustive:

- R&D/SOP012 Facilitating Monitoring Visits for Clinical Trials at CUH
- CCTU/TPL030 Monitoring Plan
- CCTU/GD008 Monitoring Activities Guidance Document
- CCTU/GD066 Remote Monitoring Guide for Central Coordinating Teams
- CCTU/FRM010 Monitoring Log
- CCTU/TPL068 Monitoring Report
- CCTU/TPL061 Remote Monitoring Report
- CCTU/TPL098 Remote Monitoring Conversation Template
- CCTU/SOP040 Risk Assessment Process for CTIMPs
- Trial Risk Review Table
- CCTU/TPL069 Close out Monitoring Report

- CCTU/SOP002 Pharmacovigilance Process for Investigator Teams
- CCTU/SOP015 Trial Master File / Site Files Essential Document Management
- CCTU/SOP018 Handling of Protocol and Regulatory Non-Compliance in Clinical Trials
- R&D/SOP003 Serious Breach of Protocol or GCP in CTIMPs
- CCTU/SOP007 CCTU Escalation Cascade
- R&D/POL002 Research Misconduct Policy

6. Summary of Significant Changes

Inclusion of Monitoring Escalation Pathway Guidance and Flow Diagram

7. Method

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

This SOP should be used in conjunction with CCTU/GD008 Monitoring Activities.

7.1. Scope of Monitoring

- Monitoring activities will be performed in accordance with the trial specific Monitoring Plan for the following:
  - All Cambridge-Sponsored CTIMPs
  - All participating Sites
  - Trial Coordination Offices/Teams (e.g. TMF)
  - Central facilities & Equipment
  - Local site facilities
  - Vendors as required
  - All stages of the trial from activation to close-out (site and trial level)
- The extent of monitoring and the frequency of visits is determined by the risk factors identified and documented in the trial specific Risk Assessment carried out according to CCTU/SOP040
- Monitoring activities will be identified and implemented based upon risk. In most cases remote monitoring activities are the first-line approach with escalating triggered on-site monitoring activities planned based upon identified risk thresholds

7.2. Selection and Qualifications of Monitors

- Monitors are appointed by and work on behalf of the Sponsor
- Monitors should be appropriately trained, and possess adequate scientific and/or clinical knowledge to monitor the trial
- Monitors will be expected to acquire adequate knowledge in order to perform monitoring activities
- Prior to undertaking any monitoring activities Monitors must thoroughly familiarise themselves with:
  - The trial IMP(s)
  - The trial protocol

- Trial processes
- Written informed consent documents
- Other trial documents
- CCTU SOPs, GCP and other applicable regulatory requirements

7.3. Responsibilities

- The Regulatory and Quality Manager and the Senior Clinical Trials Monitor use the information from the Trial Risk Assessment CCTU/FRM021 and following discussions with the CI, Trial Coordinator and Trial Monitor populate the Trial Risk Review Table.
- CCTU CTMs are responsible for developing the trial specific monitoring plan in collaboration with the trial team, based upon the Trial Risk Review Table
- CTMs monitor all Cambridge-sponsored CTIMPs in accordance with the approved trial specific Monitoring Plan.
- CTC or delegate is responsible for initiating the remote Monitoring of participating sites as determined by the trial specific Monitoring Plan
    - Remote monitoring is conducted via the Remote Monitoring Report and the Remote Monitoring Conversation Template.
- In some cases on-site monitoring may be undertaken by the CTC, depending on training and availability, under the guidance and overall supervision of a CCTU CTM
- A CCTU CTM will review the monitoring report (remote, remote conversation and on-site) completed for monitoring /activity by the coordination team, Departmental or External Monitor in order to maintain oversight of activities at participating sites
- CCTU CTM will review non-compliance report forms CCTU/FRM013 as received and the non-compliance log CCTU/FRM042 within the timelines set out in the Monitoring Plan CCTU/TPL030. This will form part of the trial central monitoring (See monitoring plan for other central monitoring activities)

7.4. Monitoring Plan

- Every trial must have a Trial Specific Monitoring Plan
- The Monitoring Plan will be based upon the information from the Trial Risk Review table
- The initial draft monitoring plan will be sent to the trial team for review and consideration of appendices inclusions
- A meeting should be scheduled between the CTM and the trial team to discuss, complete and finalise the monitoring plan, including agreeing responsibilities (appendix 2), Triggers for monitoring activity (appendix 3) and non-compliance categories (appendix 3)
- For multi-centre trials, monitoring activities at participating sites must be included in the Monitoring Plan with input from the trial team, including but not limited to:
    - Type of monitoring activities undertaken (remote conversation, remote report and triggered/scheduled on-site monitoring)

  - The frequency of each monitoring activity (Appendix 2 in trial monitoring plan)
  - Triggers for on-site monitoring (Appendix 3 in trial monitoring plan)
- The Monitoring Plan must be finalised and implemented prior to trial activation

7.5. Remote Monitoring Conversations

- Only use the Remote monitoring conversation template CCTU/TPL098 for formal remote monitoring of ongoing trials. This can be via teams/zoom/conference calls
- Remote monitoring conversations are performed primarily by the central trial team in accordance with the timelines stipulated in the Trial Monitoring Plan however they can also be used by the clinical trial monitor to record remote conversation discussions they have with the participating sites and or the coordination teams
- All completed Remote Monitoring Conversation Forms must be provided to the Clinical Trial Monitor by the central trial team for review within 5 calendar days of receipt from the participating site
- The Clinical Trial Monitor will review the form within 21 calendar days and report all findings back to the Central Trial Team for liaison with the participating site
- Feedback should be provided to the participating site in writing, in a timely manner but no longer than 5 calendar days following completion of review
- The central trial team (CTC & CI) should also be copied into the correspondence as appropriate (e.g. for central facilities, vendors or participating sites with significant findings of concern)

7.6. Remote Monitoring Reports

- CCTU/TPL061 will be used to record remote monitoring activities
- Remote monitoring is performed by the central trial team in accordance with the timelines stipulated in the Trial Monitoring Plan
- Failure to complete the remote monitoring within the timelines set must be escalated to the Clinical Trial Monitor
- The Clinical Trial Monitor can escalate any concerns with Remote Monitoring, or lack thereof, in accordance with CCTU/SOP007
- If a participating site reports they are unable to comply with the remote monitoring activity request, this must be escalated to the Clinical Trial Monitor and an alternative monitoring solution found (e.g. on-site monitoring undertaken by the departmental monitor)
- All completed Remote Monitoring Reports must be provided to the Clinical Trial Monitor by the central trial team for review within 5 calendar days of receipt from the participating site
- Review of the Remote Monitoring Report will be undertaken as stipulated in appendix 1 of CCTU/GD066 Remote Monitoring Guidance for the Central Coordination Team

- The Clinical Trial Monitor will review the Report within 21 calendar days and report all findings back to the Central Coordinating Team for liaison with the participating site
- Feedback should be provided to the participating site, in writing, in a timely manner but no longer than 5 calendar days following completion of review
- The central trial team (CTC & CI) should be copied into the correspondence as appropriate (e.g. for central facilities, vendors or participating sites with significant findings of concern)
- Copies of all remote monitoring documentation and associated correspondence must be filed in the participating sites ISF, TMF and Sponsor file

7.7. On-site Monitoring Visits

To schedule a monitoring visit, the following process must be followed:

- Contact the relevant trial team (e.g. the participating site team, coordination team, central facility team and/or other relevant departments) in advance to schedule a monitoring visit.
- For CUH on site visits only follow R&D/SOP012 Facilitating Monitoring Visits for Clinical Trials at CUH
- Identify and notify the trial team and/or other relevant departments which documents are required on the day(s) of visit
- If applicable inform the trial team of the selected participants medical notes required for the visit
- During the visit, liaise with relevant members of the trial team to obtain any missing, previously requested data, documentation and information in order to complete as much of the planned monitoring activity as possible
- At the end of the monitoring visit, the monitor will arrange a meeting with the trial team. It is expected that the PI/CI (for site visits) is available either in person or remotely to attend this meeting
    - Preliminary findings will be discussed as well as any suggestions for improved processes where systematic issues are noted by the monitor
    - Minutes are not generated for this informal meeting. It is an opportunity for the trial team to share any sensitive feedback with the Monitor such as ongoing resource issues or concerns about trial conduct

7.8. Findings

- Monitoring findings will be documented in the on-site Monitoring Report
- In the event of non-compliance with the protocol or regulatory requirements refer to CCTU/SOP018 Handling of Protocol and Regulatory Non-Compliance
- In the event of any suspicion of a serious breach of protocol or GCP, Monitors must report findings in accordance with R&D/SOP003 Serious Breach of Protocol or GCP in CTIMPs
- In the event of any suspicion of fraud of misconduct, Monitors must report findings in accordance with R&D/POL002

- In the event of any EPIC functionality or EPIC process findings the Monitors will collate and report findings in accordance with CCTU/SOP007 CCTU Escalation Cascade
- All other issues that require escalation refer to CCTU/SOP007 CCTU Escalation Cascade

7.9. On-site Monitoring Reports

On-site monitoring activity will usually span a number of days, possibly a couple of weeks depending on the complexity of the trial. Upon completion of a monitoring visit, the Monitor will:

- Complete a Monitoring Report
    - Routine/ triggered monitoring use CCTU/TPL068
    - Close Out Monitoring use CCTU/TPL069
    - CCTU Monitoring Activities Tracker is available upon request from CCTU Monitors
- Document the findings in follow up correspondence for the trial team
    - The CTM will submit both documents to the Regulatory & Quality Manager or designee for review
    - The Departmental monitor/CTC will submit both documents to the allocated Clinical Trial Monitor for review
    - External monitors will submit the agreed monitoring documentation, as defined in their service agreement to the relevant person as defined in the Trial Monitoring Plan for review
- Finalise Monitoring Reports and follow up correspondence following review and be signed as appropriate
- Provide the trial team with follow up correspondence in writing via email
- The central trial team (CTC & CI) should also be copied into the correspondence as appropriate (e.g. for central facilities, vendors or participating sites with significant findings of concern)
- File the original signed report and copies of correspondence in the Sponsor File. The Sponsor file will hold all monitoring reports for all sites, regardless of who generated them, to demonstrate Sponsor Oversight of the trial and compliance with the Monitoring Plan
    - A copy of any monitoring report generated by the CTC or delegate (not the sponsor monitor) will also be retained in the TMF as evidence of trial team activity

7.10. Monitoring Escalation Pathway Guidance and Flow Diagram

This escalation pathway is designed for Cambridge Sponsored CTIMPs.

It can be used as a guide for other CCTU managed trials however the roles for escalation should be adjusted for the trial in question.

The escalation pathway is relevant for monitoring findings from all monitoring activities (remote, onsite and central).

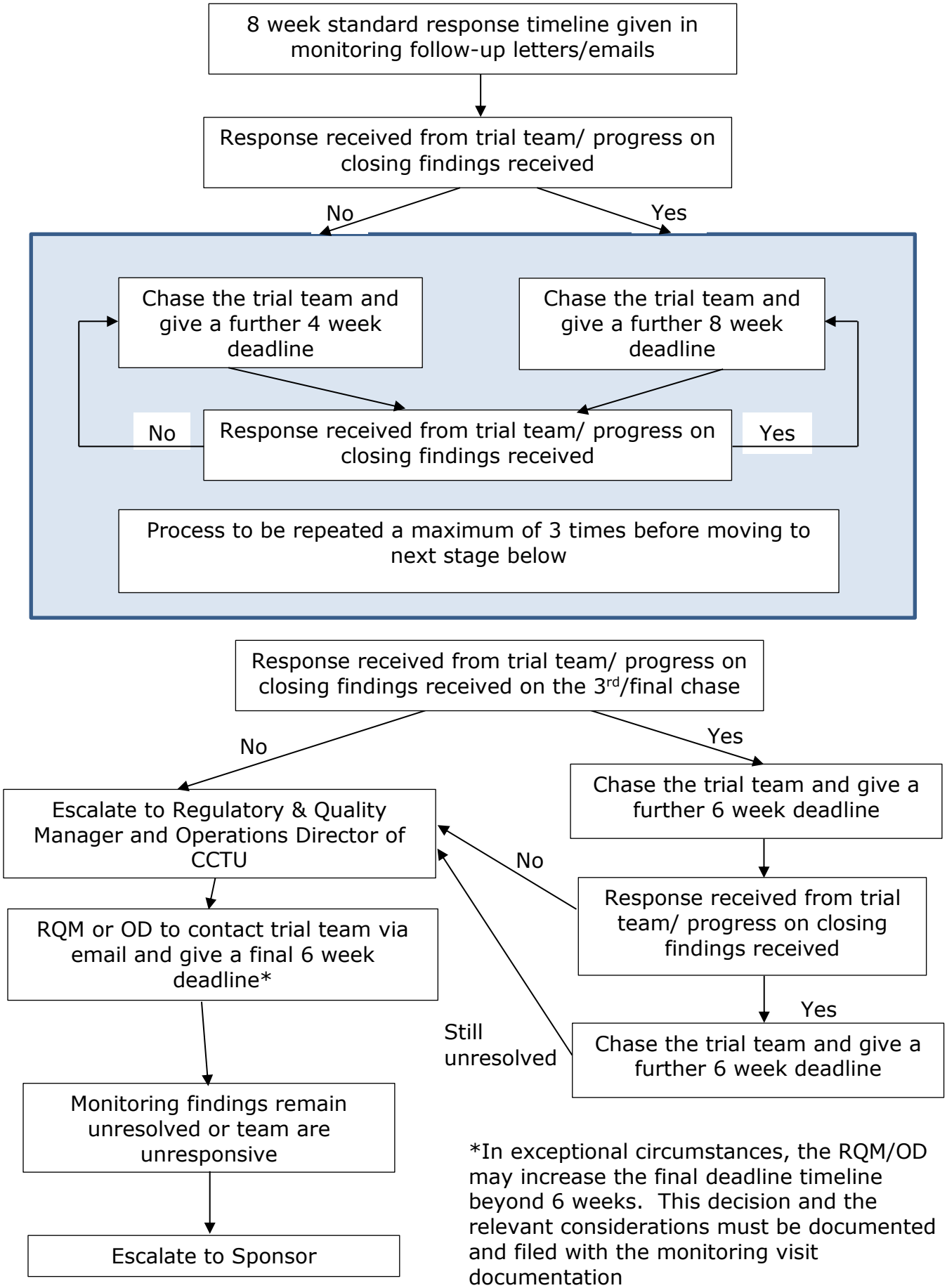
Urgent issues are managed outside escalation pathway and timelines. For example:

- Eligibility findings must be queried immediately with the relevant team

- SDV in advance of a planned data lock or report download will be subject to their own timelines

The escalation pathway is relevant for outstanding monitoring findings. Once all the findings have been suitably resolved or an acceptable response received, the monitoring visit can be closed then the escalation pathway stops.

- In general, the maximum time for findings to be resolved prior to sponsor escalation is 50 weeks, with a minimum of 26 weeks
- In exceptional circumstances these timelines can be reduced or increased by the Regulatory & Quality Manager and/or the CCTU Operations Director
- All decisions to deviate from the timelines stipulated in this escalation plan must be fully documented and filed with the monitoring visit documentation



*In exceptional circumstances, the RQM/OD may increase the final deadline timeline beyond 6 weeks. This decision and the relevant considerations must be documented and filed with the monitoring visit documentation

7.11. Pharmacy Monitoring for Blinded Trials

- A single monitor will be allocated to a trial
- There will be no blinded/unblinded separation of monitoring
- The monitor will not send any correspondence to the trial team that could potentially unblind the team to the treatment allocation of trial participants

7.12. Monitoring of Clinical Studies (non-CTIMPs) or Externally Sponsored CTIMPs

This SOP is specifically for CTIMPs. However, the same principles and activities apply when monitoring clinical studies or externally sponsored CTIMPs in the absence of other procedures.

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"

10. Associated Documents

NA

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:	CCTU/SOP011 version 12
Local reference:	CCTU/SOP011 version 13