

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 (R3) 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 / modification(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 sites. 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	The operational techniques and activities undertaken 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 modifications, SOPs, GCP and the applicable regulatory requirements
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
Participating site	'means a hospital, health centre, surgery or other establishment, or facility or premises at or from which a clinical trial, or any part of such a trial, is conducted' UK Clinical Trials Regulations. For the purposes of this SOP, the term Participating Site is used operationally to refer to a Trial Location. Use of the term Participating Site does not modify or replace the regulatory definition of Trial Location, nor does it alter any associated regulatory obligations.
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
CCTU	Cambridge Clinical Trials Unit
CI	Chief Investigator
CTC	Clinical Trial Coordinator
CTIMPs	Clinical Trials of Investigational Medicinal Products
CTM	Clinical Trials Monitor
CtQ	Critical to Quality
DM	Data Management
GCP	Good Clinical Practice
IMP(s)	Investigational Medicinal Product(s)
ISF	Investigator Site File
PI	Principal Investigator
SDV	Source Data Verification
SOP	Standard Operating Procedure
TMF	Trial Master File
TMG	Trial Management Group
TSC	Trial Steering Committee

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/GD073 Critical to Quality Factors Form Guidance
- CCTU/TPL068 Monitoring Report
- CCTU/TPL061 Remote Monitoring Report
- CCTU/TPL098 Remote Monitoring Conversation Template
- CCTU/SOP040 Risk Assessment Process for CTIMPs
- CCTU/TPL104 Source documentation/Data location table
- CCTU/TPL069 Close out Monitoring Report
- CCTU/SOP002 Pharmacovigilance Process for Investigator Teams
- CCTU/SOP015 Trial Master File / Site Files Essential Records 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

Update to quality control and monitoring definitions. Addition of Critical to Quality Factors Guidance document. Removal of reference to monitoring log. Changed Amendment to modification. Changed essential documents to essential records

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

- Monitoring should be conducted by persons who are not involved in the clinical conduct of the trial at the participating site that is being monitored, however the participating site staff are required to respond to remote monitoring questions either verbally for remote monitoring conversations or written/typed for remote monitoring full forms
- 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

- CCTU CTM in conjunction with the CTC is responsible for preparing the Source documentation/Data location table (CCTU/TPL104) during the trial set up stage. It should include data identified as a critical to quality factor (CtQ)
- CCTU CTMs are responsible for developing the trial specific monitoring plan in collaboration with the trial team, based upon the trial risk assessment, and meetings with the trial team prior to the finalisation of the risk assessment
- CTC or delegate is responsible for providing a copy of the monitoring plan and the Source documentation/Data location table (CCTU/TPL104) to the participating sites and requesting the site complete and return the source documentation/data table (CCTU/TPL104)
- CTMs monitor all Cambridge-sponsored CTIMPs in accordance with the approved trial specific Monitoring Plan and applicable monitoring procedures
- CTMs are responsible for preparing each type of the remote monitoring documents - Remote monitoring conversation (CCTU/TPL098) and Remote monitoring forms (CCTU/TPL061). This involves tailoring the monitoring templates to the trial taking into account the stage of the trial and in the

case of the remote monitoring conversation the trigger for the monitoring activity (eg. Routine monitoring at set timeline, recruitment of first participant(s), high number of patient withdrawal at a site). The monitoring triggers are detailed in the trial 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 within the timelines set out in the Monitoring Plan CCTU/TPLO30. This will form part of the trial central monitoring (See monitoring plan for other central monitoring activities)
- The TMG and or TSC will review the non-compliance logs periodically to identify any systematic training needs, trial or site issues

7.4. Monitoring Plan

- Every trial must have a Trial Specific Monitoring Plan that is tailored to the trial's potential safety risks, the risks to data quality and/or other risks to the reliability of the trial results
- The Monitoring Plan will be based upon the information from the Trial Risk Assessment and knowledge gained in the meetings prior to the finalisation of the risk assessment.
- The plan should describe the monitoring strategy, the monitoring activities of all the parties involved, the various monitoring methods and tools to be used, and the rationale for their use. The monitoring strategy should ensure appropriate oversight of trial conduct, and it should consider site capabilities and the potential burden. The monitoring plan should focus on aspects that are critical to quality, and it should reference the sponsor's applicable policies and procedures. Monitoring of important data and processes (e.g., those related to primary endpoints and key secondary endpoints and processes intended to ensure participant safety) performed outside the investigator site (e.g., central image reading facilities, central laboratories) should be addressed in the monitoring plan.
- 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 (this will include staff with specialist areas of knowledge if trial parameters are outside those of standard of care for example as radiologists, pathologists, radiopharmaceuticals, central facilities) to discuss, complete and finalise the monitoring plan, including agreeing responsibilities for the monitor and trial team, Triggers for monitoring activity (appendix 2) 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
 - Triggers for on-site monitoring (Appendix 2 in trial monitoring plan)
- The Monitoring Plan must be finalised and implemented prior to trial activation
- The monitoring plan (CCTU/TPL030) and the source documentation/Data location table (CCTU/TPL104) must be sent to participating sites prior to site activation
- If the monitoring plan is updated in the duration of the trial this can be sent to the participating sites.

7.5. Source document/Data location

- All sites have to complete and return the source document/data location table (CCTU/TPL104)
- The CTM and CTC are responsible for preparing the document at the trial set up stage
- The table documents the critical data for the trial including its location in the trial database and the site will ultimately complete the last column location of source data
- The document must be provided to participating sites at the site set up stage
- The Source documentation/Data location table (CCTU/TPL104) must be completed by all participating sites either as part of site set up for new sites or as part of remote monitoring for sites currently open. The site will retain a copy in the investigator site file and forward a copy to the central coordination team.
- If the Source documentation/Data location table (CCTU/TPL104) is updated during the trial, the coordination team are required to circulate to the site teams and request the sites return the updated document
- If an on site monitoring visit is triggered the sponsor assigned clinical trial monitor will request that the site provide the latest up to date copy of their Source documentation/Data location table (CCTU/TPL104) ahead of the visit

7.6. 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

- The clinical trials monitor will prepare templates for each of the remote monitoring forms and conversation forms
- The remote monitoring conversation will be tailored to the trial and to the monitoring trigger eg. routine remote monitoring at set timelines, targeted monitoring due to high number of patient withdrawals at a site, high number of primary/secondary end point data queries, etc.
- The remote conversation will be used by the coordination team to give them oversight of the trial conduct at the participating site(s) and identify any training issues or knowledge gaps at the site
- The conversation will also be used to follow-up on anything outstanding from the participating site for example data queries, previous monitoring findings, documentation gaps in ISF/SIF
- All completed Remote Monitoring Conversation Forms must be completed real time and be provided to the Clinical Trial Monitor for their review within 3 working days of the monitoring call taking place
- 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)

7.7. Remote Monitoring Reports

- CCTU/TPL061 will be used to record remote monitoring activities
- The clinical trials monitor will prepare a template for each of the remote monitoring activities. This will be tailored to the trial. This will be provided to the CTC in advance of any monitoring activity
- 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 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

7.8. On-site Monitoring Visits

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

- Inform the CI/CTC that an on-site monitoring visit has been triggered for the named participating site or facility, ask if there are any concerns or outstanding actions relating to the site/facility that the monitor should be aware of in advance of the visit.
- 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.
- Request any documents from the site/facility team that can be reviewed remotely, ahead of the visit. For example: Up to date delegation and training logs, PI's current CV and GCP, anonymised recruitment/screening log, current participant status log, selected accountability logs, destruction logs, inventory logs, sample storage logs, local SOPs etc.
- Prepare in advance for the visit by reviewing the modification trackers and collate a list of the approved versions of each of the trial documents, where this isn't provided by the CTC.
- If applicable inform the trial team of the selected participants medical notes required for the visit also check that the sites Source documentation/Data location table (CCTU/TPL104) is up to date by e-mailing the site a copy held by the coordination team and asking the site to confirm if it is still current.
- During the visit, prioritise the monitoring activity against the monitoring trigger. This can be deviated from if you have concerns 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

7.9. Findings

- Monitoring findings will be documented in the relevant Monitoring Report
- In the event of non-compliance with the protocol, SOPs or clinical trial regulations refer to CCTU/SOP018 Handling of Protocol and Regulatory Non-Compliance
- In the event of any suspicion of a serious breach of protocol, GCP or clinical trial regulations, 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 or misconduct, Monitors must report findings in accordance with R&D/POL002
- In the event of any CUH EPIC functionality or CUH 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

7.10. On-site Monitoring Reports

On-site monitoring activity will usually take a day for participating site/facility monitoring or it could span a number of days for coordination team monitoring. This will depend on the complexity of the trial, and the reason for the monitoring activity (routine or triggered). 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

The CTM will file responses to the monitoring findings in the sponsor file, the site/facility being monitored must also file responses in their own folders (TMF, ISF, DM file, Statistics folder etc.)

7.11. 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.

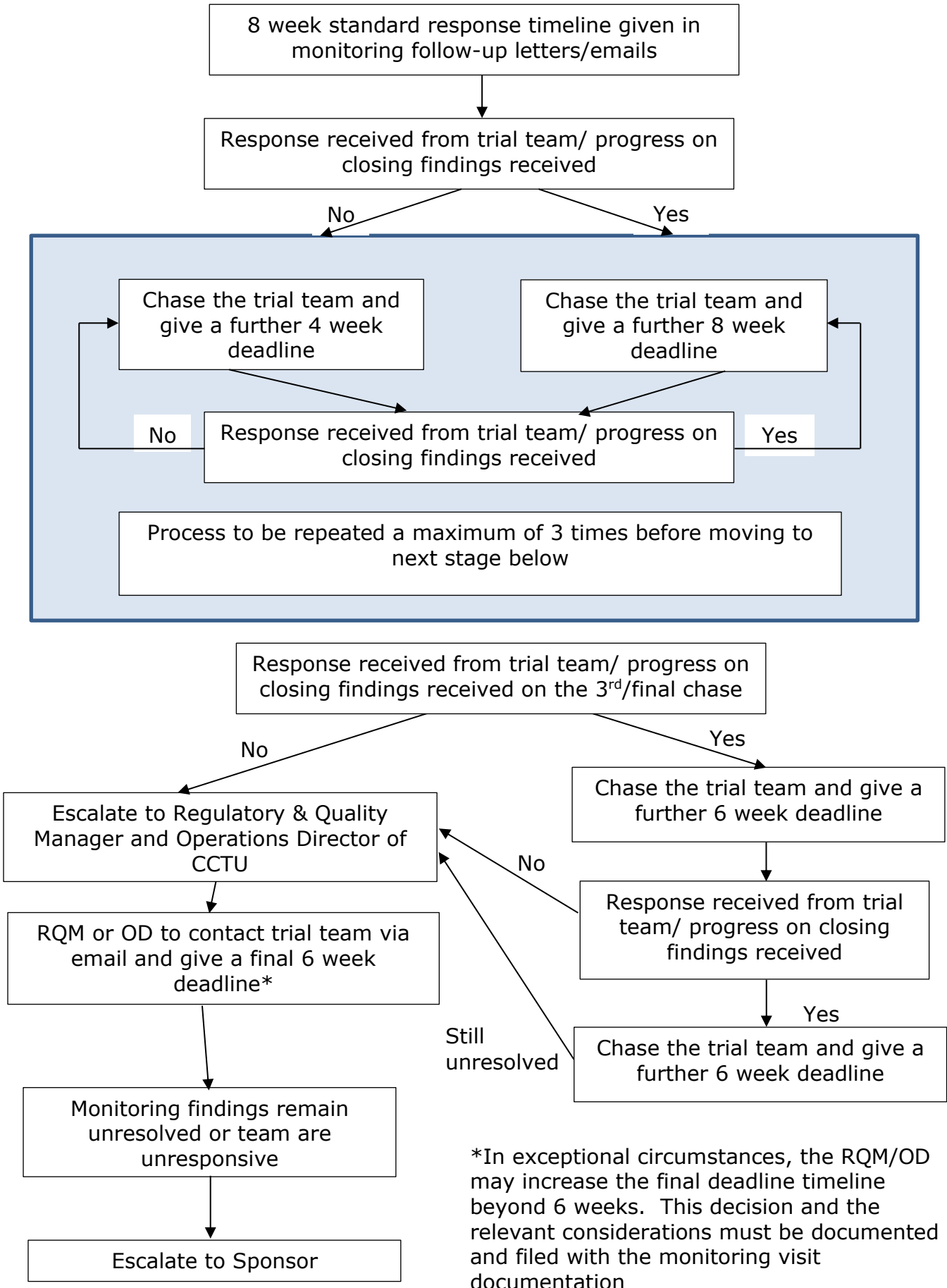
The escalation pathway is relevant for monitoring findings from all monitoring activities (remote, onsite and central).

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



7.12. Pharmacy Monitoring for Blinded Trials

- A single monitor will be allocated to a trial (some larger trials may have 2 monitors)
- There will be no blinded/unblinded separation of monitoring
- The monitor(s) will not send any correspondence to the trial team that could potentially unblind the team to the treatment allocation of trial participants

7.13. 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

Common Abbreviations and Definitions CCTU/INF001
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.

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