CCTU Monitoring Activities Guidance Document

This guidance document is to be used in conjunction with CCTU/SOP011.

This document can be used as a reference document for other staff required to perform monitoring activities. Please discuss with CCTU Monitors.

Monitoring
ICH Topic E6 (R2) – “Guideline for Good Clinical Practice” defines monitoring as 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, written procedures, Good Clinical Practice, and the applicable regulatory requirement(s).

Trial Risk Assessment and forming a Trial Monitoring Plan
A monitoring plan for each trial will be completed prior to trial initiation.
When writing a monitoring plan, the monitoring frequency and activities should be in line with mitigating actions identified in the risk assessment of the trial.

Risk assessment is an on-going process throughout the life of a trial. If the risk of a trial changes, which necessitates changes to monitoring requirement for that trial, the monitoring plan and risk assessment should be updated to reflect the change in monitoring activities. The updated monitoring plan and risk assessment will be sent to the coordinating team for review.

Monitoring Visit Types

Pre-Initiation
Prior to trial initiation, the TMF, ISF including applicable support departmental files, such as Pharmacy file, Clinical Research Facility file, will be reviewed to verify that the trial can be initiated at the lead/coordinating site.

Verify
- Applicable support department set up is complete, including all guidelines in place
- IMP(s) supply is arranged or can be arranged immediately after R&D approval is issued in cases where IMP is shipped from manufacturer or from a different site
- All trial documents are accurate and in place for the trial to commence recruitment, although it is possible that there will be some degree of finalisation made to some documents after the initiation visit
- Ensure there is an adequate supply of trial material in place for the trial to be conducted in accordance with the protocol

If there are any findings from this review which would suggest the trial is not ready for initiation, this must be notified to the designated Clinical Trials Officer. Initiation should only take place when the set-up is deemed complete and the site can commence recruitment immediately upon initiation.

Sponsor Initiation
The initiation meeting is led by Clinical Trials Officers, but the Monitor will be present to go through any monitoring related issues. The Monitor must be able to verify the
completion of outstanding items from pre-initiation TMF review either prior to or during Trial Initiation.

**Routine Monitoring**
Monitoring visits will be carried out in accordance to the monitoring requirement set out in the Monitoring Plan, verifying
- That the safety, rights and well-being of trial subjects are protected
- Trial team delegation is appropriate and members are suitably trained
- Processes are consistently followed and activities are consistently documented
- Trial data are accurate, complete and verifiable against source documents
- The conduct of the trial remains compliant with the approved protocols (and amendments if applicable), GCP and applicable regulatory requirements

**Trial Close Out**
Trial close out monitoring will be completed after the end of trial has been declared to both the MHRA and REC. This should preferably be carried out after the end of trial report is submitted and results uploaded to EudraCT database. However, local site close-out can happen before this. All documents will be reviewed to ensure they are ready for archiving, i.e. there are no outstanding issues.

Trial close out monitoring must be completed for all CTIMPs that have obtained/received IMP even if no patients were recruited. The Pharmacy Sponsor File (if available) should also be collected and handed to the Clinical Trials Officers for reconciliation with the Trial Sponsor File in preparation for Sponsor archiving.

Verify
- All documents, including documents maintained by other departments, are filed in the appropriate trial file, and file notes are present to provide explanation for missing documents
- End of trial notifications are submitted and filed
- End of trial reports are/will be submitted and filed
- All data queries have been resolved
- Source data have been filed appropriately
- Investigator is aware of on-going commitment

Refer to CCTU/SOP004

Trials closed to the MHRA but remaining open to the REC require routine monitoring at a reduced frequency. The monitoring plan will be updated to reflect any changes to the monitoring activities.

**Prior to Monitoring Visit**
Aside from scheduling the monitoring visit and notifying the trial team of the required documents for the monitoring visit, the monitors should also complete the following in preparation of the monitoring visit
- Review previous monitoring reports and follow up correspondence, if available, or audit reports, together with any other documents which may indicate items requiring follow up
- Be familiar with the most current approved protocol
- Check the trial status with the trial team (amendments, recruitment update).
The Sponsor File can also be reviewed in preparation of the monitoring visit.

Legal documents, such as agreements are maintained by the Legal team in R&D and can be accessed if necessary.

Prepare monitoring tools, such as
- Copy of previous file review checklist
- Listing of SAEs/SARs/SUSARs from Pharmacovigilance database

When scheduling a monitoring visit arrange a time to meet with the key team members where possible.

**During a Monitoring Visit**

The monitoring activities completed at any particular visit will depend on the trial status and requirement according to the monitoring plan. Expected monitoring activities include but are not limited to:

- Informed Consent Documents (ICD) and eligibility review
- Source Data Verification (SDV) and Case Report Form (CRF) review
- Investigational Medicinal Products (IMPs) management review
- Research sample/laboratory management review
- Review of ACRC|CCRC documents where applicable
- Follow up of serious breach Corrective and Preventative Actions (CAPA) where applicable
- Review items for follow up from previous activities to check for completion
- Essential documents review

**Informed Consent Documents (ICD) and Eligibility Review**

Review of informed consent documents and the eligibility of enrolled participants, including review of documentation in source, must be carried out for all CTIMPs. The percentage reviewed is specified in the trial monitoring plan.

The purpose of informed consent document review is to ensure

- All participants entering trial screening have been provided with written informed consent prior to any trial related procedures being carried out
- The consent process conforms with GCP and regulatory requirements and is consistent with the consent procedure detailed in the REC form or protocol
- The consent process is documented in participant’s source documents

The Monitor should verify

- That the original signed informed consent (including all superseded versions if re-consent was necessary), with the participant information sheet, for each screened participant are filed in the TMF (or site file as applicable)
- The correct and approved version of consent documents were used at time of consent
- The consent procedure is adequately recorded in the participant’s source documents - how the participant was identified, approached, when was PIS given to participant for consideration, the discussion that took place, date of consent and if that was prior to trial related procedures
- The participant and the person taking consent personally sign and date the consent form
- The date of consent correlates with the visit date
- A copy of the informed consent documents is filed in the participant’s source documents
- If applicable the re-consent process and documentation is timely and appropriate
- The review and outcome of participant eligibility is sufficiently documented
- Only eligible participants are enrolled based on available documentation
- That trial number is allocated and documented in the source documents

**SDV and CRF Review**

The percentage of SDV and CRF review completed for each trial is determined by the risk assessment of the trial and trial team experience.

The purpose of SDV and CRF review is to ensure
- Data collected on the CRF is completed in a legible and timely manner
- Data reported is accurate and consistent with source documents
- Protocol specified visits and procedures are conducted as detailed in the protocol
- Non-compliance to the protocol are identified and reported appropriately
- Queries are completed in timely manner
- All reportable events are documented and reported

The Monitor should verify that:
- Source data requirements are met
- The consent process and documentation is completed as defined in ‘ICD and eligibility review’
- Documentation of eligibility review as defined in ‘ICD and eligibility review’.
- The trial visit, date and all assessments performed are documented
- There is sufficient documentation of findings pertinent to the participant’s well-being, including medical history, physical examination and vital signs
- Laboratory reports and scans have been reviewed and the review documented in a timely fashion
- Participant identity is not disclosed on any printed documents if they are filed amongst the CRF
- There is evidence of review of AEs performed at each trial visit, that the information has been documented, including but not limited to onset/offset date, relationship to IMP, any concomitant medications taken
- Documentation of IMP management, including the date of the final trial drug administration
- There is documentation detailing the participant last visit including date, reason for early withdrawal if applicable and the plan for future management
- Communication with participant, including any phone calls is documented
- Any other information provided to the participant during visits, even if not immediately relevant to trial is documented

**IMP Management Review**

Monitoring of the Pharmacy will be carried out according to trial-specific monitoring plan. More frequent visits can be carried out according to individual trial need.
The purpose of IMP management review is to ensure that:
- The Investigator has the relevant and updated reference safety information for the IMP, such as current Investigator’s Brochure, IMPD or SmPC
- The IMP is handled according to pharmacy procedures, manufacturer’s instructions and protocol requirements
- IMP handling is only performed by delegated and appropriately trained staff

The Monitor should verify
- Appropriate documents are present pertinent to safety information for the IMP, including IB/IMPD/SmPC, Manufacturer’s Authorisation and Qualified Person release of IMP per batch
- Staff carrying out IMP related activities are on the signature list and have been appropriately trained
- The IMP used is consistent with approved IMP as per CTA
- The IMP labelling is consistent with labels approved by the MHRA
- The IMP is stored in accordance to trial IB/SmPC
- Shipment documents are present if IMP was sent from the manufacturer, such as a delivery note
- The IMP is correctly dispensed according to protocol requirements and for enrolled patients only, including randomisation if applicable
- Masking of treatment is maintained if applicable
- Documents are present to support dispensing, such as a list of participant, prescriptions, worksheets, inventory logs, accountability logs
- Temperature excursions are correctly documented and escalated if appropriate, and affected IMP stock is correctly handled and documented
- Appropriate documentation is in place for any returned or destroyed stock, such as shipment confirmation, destruction certificate
- The IMP accountability is consistent with the starting stock, dispensed quantity, and quarantine/return/destroyed IMP
- There is sufficient quantity of IMP on site within expiry date for continuation of the trial

Research Sample/Laboratory Management Review
Monitoring of laboratory and sample management should be carried out according to the risk of the trial and the endpoints that the sample analysis supports (for example, Primary Pharmacokinetic endpoints or exploratory translational endpoints).

The purpose of sample/laboratory management review is to ensure
- Research samples are collected, processed and stored appropriately according to protocol and trial requirements
- Movement of samples are in accordance to protocol and laboratory manual
- Long-term storage of samples are carried out according to REC approval

The Monitor should verify that
- Samples are collected and stored only for participants who have given consent
- Participant requests for samples to be destroyed are carried out
- Accurate records of samples collected, processed and storage location are kept
- Samples are stored in appropriate temperature-monitored locations
- Any temperature excursions are reported and documented, and appropriate actions taken
- Sample shipments are documented

**Essential Documents Review**

The TMF/ISF, including support department files such as pharmacy file and ACRC study folder, should be reviewed as appropriate at monitoring visits. A file review checklist can be used to document the review, recording documents that are present and those that are missing.

The purpose of the essential documents review is to ensure that:

- All necessary approvals are in place prior to commencement of recruitment activities
- Amendments, if any, are only implemented after all approvals are in place
- The Investigator is complying with regulatory requirements in relation to provision of necessary reports in order to maintain the approvals
- The trial has all the required materials, including current CRF, consent documents, logs to ensure the conduct of the trial is accurately documented
- The binders identify the trial appropriately and in an orderly fashion, and are stored securely
- Appropriate data management processes are in place
- Participant confidentiality is maintained
- The PI is maintaining sufficient oversight of the trial
- The file is “inspection-ready”

The monitor should verify

- Documentation of all submission and approvals to all relevant bodies are filed and any remarks given have been addressed
- Annual reports are submitted in the specified timeframe to all relevant parties
- The trial team is working to the latest approved protocol and has the most current reference safety information on the IMP, such as the latest IB, IMPD or SmPC. For IBs, annually update is expected or a note from the manufacturer to confirm no update is required
- Evidence of documenting and reporting of non-compliance to GCP, SOP or protocol
- The delegation log is up-to-date and accurately reflect members of the trial team and their delegated responsibilities
- The qualifications and training (including trial-specific and GCP training) for all delegated members of the trial team is documented and valid at all times throughout the trial
- Reportable events have been appropriately documented and reported according to regulatory requirements and Trust SOPs
- The participant screening/enrolment status is accurately reflected on the various trial logs and consent documents
- Participant identifiable information is not present in any documents other than the signed informed consent and the subject ID log and not for any non-trial participant
- The latest approved versions of participant consent documents are used
- Research/laboratory samples, if applicable, are correctly tracked and handled
- If specific equipment’s are being used for the trial, maintenance and calibration records are maintained throughout the trial
- A copy of the trial non-compliance log should be obtained at each visit to be filed in the Sponsor file

**After a Monitoring Visit**

A report and follow up letter will be completed normally within 15 working days from last monitoring activity. Whenever possible, data should be entered into the monitoring report during the monitoring visit. The report must clearly document all the activities completed and findings from the monitoring visit. Because the monitoring report will not be send to the Investigators, the follow up correspondence must also clearly record all findings and actions required.

Findings which do not fall into an appropriate section in the report are recorded in a general comments section.

As a minimum, the following findings are expected to be listed in the monitoring report and follow up letter:
- Trial status update, including recent or upcoming amendments and approval status, participant recruitment status
- Missing documents from the TMF/ISF review
- Issues on delegation, training of staff and related documentation, such as CV, GCP training, trial specific training
- Issues on compliance to submission of annual reports and other communication with MHRA, REC, R&D and HRA
- Non-compliance to protocol, GCP or SOPs
- Issues noted in relation to the consent process and documentation
- Issues on pharmacovigilance reporting
- Issues on trial source data and CRF
- Issues on IMP management and documentation
- Issues noted on research samples/laboratory management
- Outstanding actions from previous monitoring visits
- Whether conduct of trial results in change in monitoring frequency or requirement

Monitoring report must clearly list all items for follow up, the follow up letter must include recommended actions in order to assist trial team to complete issues identified.

**Review of Completed Monitoring documents**

The Regulatory and Quality Manager (RQM) (or delegate) will complete a review of the report and follow up letter. Prior to the review, the RQM should be notified of the report and letter due date. A minimum of 3 working days should be allowed for this review.

**Filing of Monitoring Documents**

Monitoring reports must be signed by the author and reviewers upon finalisation, a copy together with the follow up letter and any other related documents and emails confirming date sent must be filed in the Sponsor File.
Review of Monitoring Reports from External/Departmental Monitors
For trials which have external/departmental monitors carrying out monitoring visits at participating sites, allocated CTM or delegate will be responsible for the review of monitoring visit report and related correspondence from the visit. These documents must be filed in the Sponsor file.

The Monitor who completed the report should be contacted for clarifications significant issues identified from the review of the reports should be discussed with the Regulatory and Quality Manager if the review is completed by a CTM.

Review of Remote Monitoring Reports
Multi-centre trials are required to carry out remote monitoring of participating sites according their trial monitoring plan. Completed remote monitoring reports will first be reviewed by the coordinating team, and subsequently sent to the CTM for review. All comments will be sent back to the coordinating team who will then follow-up with the participating site. Pertinent documents must be filed in the Sponsor file.

CCTU Monitoring Activities Tracker
There are four trackers that will need to be completed to track monitoring activities status and progress
  - Master monitoring plan
    To record proposed visit schedule according to frequency as stated in monitoring plan and actual visit dates
  - Follow up letter turnaround
    To record number of days required to send follow up letter to trial team after last monitoring activity completed. A separate spread sheet is included to record when contacts are made with trial team to set up monitoring visit
  - Monitoring finding trends used internally for trend analysis
  - External remote report review
    To record the time spent on review of remote monitoring reports