Monitoring guidance document

The purpose of this guidance document is to provide more in-depth detail of the steps, documentation and requirements for performing a monitoring visit for studies sponsored by Barts Health NHS Trust (Barts Health) or Queen Mary University of London (Queen Mary).

Contents

1. Scope

The scope of monitoring carried out under this Standard Operating Procedure (SOP) is to assess the compliance of clinical trials with the applicable legislation and guidance including the Medicines for Human Use [Clinical Trials] 2004 Statutory Instrument, 1031 and all subsequent amendments, Good Clinical Practice (GCP) guidelines, the UK policy for health and social care research, 2017, General Data Protection Regulation and the Data Protection Act 2018, and Barts Health and Queen Mary research SOPs and policies.

2. Definitions

Monitoring is defined as the act of overseeing the progress of a clinical trial and of ensuring that it is conducted, recorded and reported in accordance with protocols, amendments, SOPs, GCP and applicable regulatory requirement(s):

- On-site monitoring: Monitoring activities that are primarily undertaken during a physical visit to the investigator site by one or more monitoring personnel.
- Central and/or statistical monitoring: Monitoring activities that are undertaken by Sponsor or monitoring personnel at a location remote from the research site e.g., a data centre.
- Remote Monitoring: involves off-site review performed by the monitor away from the site at which the study is being conducted.

Chief Investigator (CI) Team: This is the team that the CI delegates some responsibilities such as coordinating the study, data management, statistics etc.

3. Monitors' Responsibilities

- Monitoring should be a designated task on the study delegation log.
- If working on the study during set-up, the monitor should attend the site initiation visit as part of their study training and familiarisation (see *SOP 46 - Site selection, site initiation and site activation*).
- The monitor (GCP and Governance Managers) will be the main line of communication between the Joint Research management Office (JRMO), Investigator(s) and site team(s) with support from the GCP manager.
- The monitor is responsible for conducting monitoring visits according to the study's monitoring plan, using the JRMO agreed monitoring tools.
- The monitor is responsible for writing the monitoring report and gaining their supervisor's approval of the report.
- The monitor will ensure that reports are disseminated to the relevant people.
- The monitor will ensure that central facility reports, i.e., central or labs or imaging, are circulated to the CI (who must have oversight of the whole study).
- The monitor is responsible for following-up with the PI/site/central facility team(s) to ensure that report findings are actioned within the report deadlines.
- The monitor is responsible for escalating findings to the GCP and Governance Manager and CI if findings are unresolved or serious. The GCP and Governance Manager will ensure that Corrective Action and Preventive actions are put in place to prevent recurrence of the deviation.
- In the event that monitoring findings are not rectified, or meetings/visits are not held in a timely manner, the monitor and the GCP and Governance manager will escalate unresolved findings or concerns, in accordance with the JRMO escalation policy.
- The monitor will immediately notify the GCP and Governance Manager in the event of any suspicion of scientific misconduct, fraud, or breach of GCP. This will be dealt with in accordance with the appropriate organisational policy and/or in accordance with *SOP 37 - Reporting serious breaches of GCP or study protocol*.
- Should any of the following come to the monitors attention, it is their responsibility to escalate the event(s) to the GCP and Governance Manager:
    - The monitor's report findings are not actioned or closed in a timely manner.
    - The study team does not adequately respond to the monitor's written requests.
    - The monitor suspects non-compliance with the regulations or GCP.
    - There is a breakdown in the communication between the study team or in the management of a study.
    - Requests for monitoring visits are obstructed or repeatedly postponed by the site team.
    - The monitoring visits are not compliant with the monitoring plan.
    - The monitor suspects that the CI or Principal Investigator (PI) or other member of the research team is not fulfilling their sponsor-delegated duties.

4. Monitoring Plan

The frequency and type of monitoring must include, but not limited to:

- the study objective,
- scope,
- design,
- phase of the study,
- number of sites,
- complexity,
- blinding,
- randomisation,
- study endpoints - i.e., what source data should be verified to meet the end points,
- Investigational Medicinal Product (IMP) (including IMP storage and shipment),
- vulnerability of the participants and the type of consent,
- experience and previous compliance of the CI,
- the experience and the extent of study management support available to the CI,
- organisational reputational risks of the study,
- and the study interventional risks.

The type and combination of monitoring can be adapted and tailored to suit a particular study. Central and/or statistical monitoring can be used to assess aspects such as site outliers, data patterns and trends across the study, early safety signal detection and early identification of sites not completing or submitting Case Report Form (CRFs) or other forms.

5. Monitoring Objectives

The objectives of the visit are to:

- Provide the JRMO and the CI with an assessment of the site's overall compliance and performance.
- To verify the adherence to the protocol procedures schedule as documented in the protocol and study manuals e.g., laboratory, imaging, pharmacy, etc.
- Verify the accuracy and completion of the data recorded in the CRFs by comparing with the original data source, as outlined in the monitoring plan.

6. Preparing for a visit

The monitor must review the relevant study documentation prior to the visit. This includes, but is not limited to:

- Previous Monitoring Visit Report(s) (MVR) and/or audit report(s) (to ensure that previous findings have been closed).
- Any Serious Adverse Event (SAEs)/ Suspected Unexpected Serious Adverse Reaction (SUSARs.)
- Monitoring plan (to assess compliance).
- Recent correspondence.
- Latest version of the protocol.
- Recent amendments.
- CRFs (if available).
- Status of site (e.g., recruiting, in follow-up).
- Recruitment at the site (if available, i.e., from the sponsor's database, previous monitoring reports).
- Minutes of study committee meetings and evidence of other critical decision-making.

7. Monitoring findings

Classify the monitoring report findings.

All MVR findings will be classed as either Critical, Major or Other and also sub categorised based on the deviation area. Categorisation is as followed:

1. Essential documents:
   a. Study
   b. Approvals
2. Vendors / contracts / subcontractor/ finance
3. Informed consent procedures
4. Inclusion and exclusion criteria
5. IMP and non-IMP
6. Training and staffing
7. Deviation study procedures
8. Pharmacovigilance
9. Randomisation and cohort allocation/un-blinding
10. Data management (source data and CRF)
11. Study equipment
12. Computer systems
13. Deviations to GCP/regulations

8. Findings escalation

8.1 Documenting monitoring findings.

Following each monitoring visit, the JRMO Clinical Trial Monitor will prepare a monitoring report which will include a list of findings, and the deadlines for resolving the findings. The monitoring report will be sent to the study team, along with a separate summary of findings table. The study team must complete the summary of findings table to document the actions they have taken to address the findings and return it to the monitor within the specified deadlines.

Once the monitoring report has been sent to the study team, the clinical trial monitor will enter the visit findings into the Findings Tracker spreadsheet, located in the JRMO Governance Team shared drive. The Findings Tracker spreadsheet is used to maintain oversight of open findings and to identify findings that are not resolved on time.

8.2 Identifying overdue findings.

The JRMO GCP team hold regular monitoring review meetings which includes a full review of the Findings Tracker. Any open findings which have passed their deadline will be flagged for escalation where extension given for resolution has not been agreed nor adhered to. The outcome of the tracker review is documented in an email and circulated to relevant members of the GCP Team. When a finding has been escalated, this is also documented on the Findings Tracker.

8.3 Escalating overdue findings.

Critical Findings: critical findings must be escalated to the trial's GCP manager and senior GCP manager if the response is overdue by one week. The trial's GCP manager will contact the study team to reemphasise the seriousness of the finding and instruct the team to provide an urgent response.

If the finding remains overdue for a further week, this will be escalated to the Research Governance Operations Manager. The JRMO Quality Assurance Manager must be notified at this stage so that the late response can be recorded on the JRMO non-compliance log as a separate non-compliance. At the discretion of the Research Governance Operations Manager, the finding may be escalated to the Sponsor Oversight Group (SOP).

Major and other findings: If a response to a finding is two weeks overdue and the study team failed to reply, the clinical trial monitor should notify the study team and CI of the late response, copying in the trial GCP manager. The clinical trial monitor should state that if a reply is not received within the next two weeks, it will be escalated. A different deadline may be set at the discretion of the clinical trial monitor and GCP manager.

If the finding remains unresolved after the deadline, the trial GCP manager will email the study team, copying the senior GCP manager (If not already allocated manager), to notify them that the finding has been escalated. The GCP manager should state that if the finding is not resolved within two weeks, it will be escalated further. A different deadline may be set at the discretion of the GCP managers.

If the finding remains overdue, this will be escalated to the Research Governance Operations Manager. This escalation will be at the discretion of the GCP manager taking into to account study teams effort for resolution. The JRMO Quality Assurance Manager must be notified at this stage so that the late response can be recorded on the JRMO non-compliance log as a separate non-compliance. At the discretion of the Research Governance Operations Manager, the finding may be escalated to the SOG.

As a note, overdue monitoring findings form part of paper 3 for the SOG meeting as per the SOG Terms of Reference.

8.4 Considerations when escalating findings.

Study teams may respond to findings, but the clinical trial monitor may determine that further action is required in order to satisfactorily close the finding. The clinical trial monitor should write back to the study team requesting further action and set a new deadline for this response. The length of the new deadline will depend on the action required but should be no longer than the original deadline for the finding.

Study teams may request additional time to resolve findings that require a lot of work to complete. With the exception of critical findings, good faith requests for extensions should be agreed. However, in most cases only one extension should be agreed per finding, and the extension should not be longer than the original deadline.

In rare cases, study teams may be unable to resolve a monitoring finding. In these cases, the study team and GCP manager should discuss the finding and decide whether the trial can continue or whether it should be halted until the monitoring finding can be resolved.

9. Logging of Summary reports within JRMO

This is the responsibility of the JRMO Monitor and GCP team. The EDGE workflow "JRMO Summary Monitoring Report" must be completed for each report reviewed.

1. All Documents should be saved as appropriate. All embedded documents should be saved separately. (See SOP 27 JRMO internal filing process for further details). Documents should be saved in BOTH the monitoring subfolder and in specific locations (e.g., Committee papers in Section 7 - Committees
2. JRMO records should be checked against the report and differences reconciled). Specifically:
    - Protocol version
    - Reference Safety Information (RSI)
    - SAEs and SUSARS
    - Amendments
    - Trial Committee meetings
3. EDGE should be updated with Site and recruitment figures. The GCP MHRA attribute should be updated.
4. REDA reminders should either be verified as correct, updated or set up to ensure that all annual and final report reminds are in place.
5. Deviation of Non-compliance should be reviewed and where appropriate the JRMO Quality Assurance manager and GCP and Governance Managers should be notified.
6. Monitoring schedule adherence should be reviewed, and significant deviations should be escalated to the GCP and Governance Managers.
7. Monitoring visits should be logged within REDA.
8. The severity and classification of monitoring findings should be reviewed, queried and escalated where needed.
9. Trial Steering Committee minutes should be reviewed, and any concerns should be escalated to the GCP and Governance Managers.
10. Review the CI's comments on overall study progress and flag any concerns to the GCP and Governance Managers.

10. Remote Monitoring

Remote monitoring and Source Data Verification (SDV) should occur only when deemed necessary by a sponsor/Contract Research Organisation (CRO) confirming that postponement of such activity would put patent safety and data integrity at risk.

The site should expect to see an updated monitoring plan outlining the key element that the sponsor wishes to SDV (for example consent, eligibility, dose escalation decision, key data points or IMP compliance).

Barts Health are not able to offer external sponsors remote access to Millennium or any of the other electronic health records systems which form part of the patient record at Barts Health.

10.1 Video conferencing with screen sharing.

MS Teams is the only approved platform for video conferencing use within Barts Health. Any other platform, software or system will need written approval from the Information Governance team (Please contact records.management@nhs.net ensuring the email is clearly marked in the subject as 'External monitoring arrangements request').

Before any remote monitoring activity occurs, the following conditions must be met:

a) The sponsor or external body has a contract with the Barts Health, or the confidentiality section of the Organisation Information Document , previously Statement of Activities) template is in use and signed(Any questions please contact the JRMO).
b) The person preforming the monitoring activity is known to the Barts Health study team
c) External sponsor or CRO has an appropriate SOP or equivalent in place to cover this activity.

Additionally, the external party/monitor should document in writing that they agree that

1) No screen shots will be taken during the screen sharing.
2) The video conference will not be recorded.
3) No printing, emailing or downloading of any records or ensure this is disabled by the system.
4) Location of access will be agreed –this must be a private location.
5) The external party confirms they are alone in the room/area and is not allowing anyone else to see their screen or overhear the conversation.
6) The device used for the video conferencing must have adequate security, such as adequate firewalls, secure log-in and passwords etc, and must not be left unattended and accessible.

It is the study PI's responsibility to ensure the above conditions are met.

Site can de-identify, copy, and verify source data and send (secure email or secure postal routes*).

If this is the preferred route the following conditions should apply:

- Sponsor or external party must have a contract or agreement in place with the site
- Address must be verified as accurate through a documented test transmission**

- Sponsor must a have a SOP or equivalent in place to describe the process and destruction of data

*Postal or courier cost should be met by the sponsor. The route used should be assessed and deemed suitable by the sponsor as a minimum recorded delivery is needed to confirm arrival.

**If this is a personal home address the Sponsor should confirm they have procedures and systems in place to allow this.