Monitoring of Research Sponsored by NuTH

NJRO-GEN-SOP-021

Contents

1. Background/Introduction

Monitoring is defined in the ICH GCP Integrated Addendum E6(R2) 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, Standard Operating Procedures (SOPs), Good Clinical Practice (GCP), and the applicable regulatory requirement(s)" (SI 2004/1031 Regulations 28 & 29).

The purpose of monitoring is to verify that:

- The safety, rights and wellbeing of all human subjects are protected.
- All investigators are appropriately selected, trained and supported to complete the clinical trial.
- The reported trial data are accurate, complete, and verifiable from source documentation.
- Processes are consistently, and all activities are correctly documented to ensure high quality trial conduct and protocol compliance.
- The conduct of the trial is in compliance with the currently approved protocol/amendment(s), with GCP, and with all applicable regulatory requirements (MHRA GCP Guide, 2012).

Monitoring is a quality control process, designed to verify the quality of a study and should not be confused with auditing which is a quality assurance procedure performed by personnel independent of the study (see NJRO-QA-SOP-001).

A monitoring plan describes the strategy, methods, responsibilities, and requirements for monitoring a study. Most monitoring plans will contain, as a minimum, verification of the existence of participants; checks for valid informed consent; checks relating to patient safety and safety reporting; checks for data quality and completeness; and checks of compliance with relevant legislation, the study protocol and relevant SOPs. However, additional requirements may be necessary depending upon the type of trial and the outcome of the study risk assessment.

2. Purpose

The purpose of this SOP is to describe the different types of monitoring procedures that can be used in clinical studies. It also details the processes to be followed for studies sponsored by The Newcastle upon Tyne Hospitals NHS Foundation Trust (NuTH) to ensure adequate oversight is maintained.

3. Scope of Document

This document should be followed by all NuTH staff involved in studies sponsored by NuTH including members of the Newcastle Joint Research Office (NJRO) who have responsibility for performing sponsorship duties.

This SOP also applies to all trial management personnel who have been delegated the responsibility of developing a monitoring plan and performing monitoring activities for NuTH sponsored studies. If Clinical Trials Units (CTUs) intend to use their own monitoring SOPs, written authorisation should be received from Sponsor prior to implementation. Any decisions will be documented in the delegation of duties agreement, which is reviewed and approved by sponsor, prior to approval being granted.

4. Definitions

The following definitions were derived from the ICH GCP Addendum (E6(R2):

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, SOPs, GCP and all applicable regulatory requirements.

Monitor: An individual who is assigned the task of monitoring the study to ensure the rights and wellbeing of human subjects are protected; the reported trial data are accurate, complete and verifiable from source documents and that the conduct of the trial is in compliance with the currently approved protocol, GCP and applicable regulatory requirements. For NuTH sponsored research, monitoring duties are often delegated to a trial management team.

Monitoring Report: A written report from the monitor to the Sponsor after each site visit and/or other trial related communication according to the Sponsor's SOPs.

Monitoring Plan: A document that describes the strategy, methods, responsibilities, and requirements for monitoring the trial.

Source Data: All information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents (original records or certified copies).

Source Data Verification (SDV): The act of checking the accuracy and completeness of the case report form (CRF) entries against the source documents in accordance with the protocol requirements.

Source Data Review (SDR): A review of source documentation to check the quality of source, review protocol compliance, ensure critical processes and source documentation are adequate.

Source Documents: Original documents, data and records (e.g. hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate copies, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories and at medico-technical departments involved in the clinical trial).

5. Roles & Responsibilities

It is the NJRO's responsibility to oversee the conduct of all NuTH sponsored studies and to ensure compliance with the approved protocol, GCP and all applicable regulations.

Where monitoring duties have been delegated to a CTU, the trial management team are responsible for developing a monitoring plan, conducting monitoring as per the approved monitoring plan and submitting monitoring reports to Sponsor in a timely manner for review.

If the monitor identifies any protocol or GCP non-compliances, they are responsible for reporting these to Sponsor in a timely manner (as per NJRO-GEN-SOP-002).
The Regulatory Compliance Team (RCT) are responsible for reviewing monitoring reports submitted for all NuTH sponsored high risk research. This includes:

- Clinical Trials of Investigational Medicinal Products (CTIMPs)
- Advanced Therapy Medicinal Products (ATMPs)
- Applicable Device Studies (including clinical investigations of non-CE marked devices)
- Randomised Surgical Trials
- International Studies (where deemed high risk)

The Research Governance Team (RGT) are responsible for reviewing monitoring reports (if applicable) for all other NuTH sponsored low to medium risk research.

The Monitor is responsible for ensuring that all outstanding actions identified during monitoring activities are followed up with sites and where appropriate Corrective and Preventative Actions (CAPA) are implemented.

6. Procedures

The procedures below reflect the process for high-risk research studies falling under the RCT within the NJRO. For all other research sponsored by NuTH that incorporates monitoring activities, appropriate arrangements will be made within the RGT on a case by case basis.

Monitoring Plan

Following completion of the NuTH Clinical Trial Risk Assessment Form (CTRAF) (see NJRO-REG-SOP-004), a study specific monitoring plan will be developed to ensure that the monitoring approach is proportionate and directed to the critical areas of risk identified. A monitoring plan will be completed for all NuTH Sponsored studies falling under the RCT. For other low-medium risk NuTH sponsored studies falling under the Governance team, this will be decided by the Sponsor team on a case by case basis.

A monitoring plan describes, in detail, the nature and extent of monitoring required for a clinical research study and is where the monitoring strategy, as agreed by the study Sponsor, is formalised.

The method of monitoring, intensity (how much of a potential item will be reviewed), the frequency of visits and focus of monitoring visits will be determined by the risk rating allocated to a study to ensure that monitoring approaches are targeted and justified, and that potential risks are mitigated where possible. Key priorities must always be the safety of participants and the integrity of study data.

Regulatory and legislative requirements and ensuring compliance with the study protocol, GCP, local policies and SOPs will also influence the type and extent of monitoring that is planned.

When determining the type and frequency of monitoring activities, the available resources (including personnel and financial) should be taken into account. It is essential that the

monitoring activities outlined in the monitoring plan are achievable and can be maintained throughout the study.

A monitoring plan template which has been approved by NuTH as Sponsor can be located here. The template can be adapted where necessary depending upon the type of study and its risk category.

If alternative templates are to be used, confirmation from Sponsor of their suitability for use must be received.

Monitoring plans must be completed for all NuTH sponsored high-risk studies and should identify the elements of monitoring to be covered and how these are to be conducted, including the adaptive and escalation aspects

The task of drafting the monitoring plan is usually delegated to the trial management team via a Sponsor Delegation of Duties Agreement. The plan should detail:

- **Types of monitoring to be used and the rationale for their selection** *(Will on-site, central, remote, internal or a mixture of monitoring methods be used? Why have these been chosen?)*

- **Standards and written procedures (SOPs) to be followed** *(Which standards or regulations will be monitored against? Are there SOPs or procedures to be followed?)*

- **Frequency and timing of monitoring** *(When will monitoring occur? Will it be scheduled for a particular time point or will it be triggered?)*

- **Details of which sites will be monitored** *(Will all sites be monitored or just a selection? If a selection, how/why/when will they be selected?)*

- **Responsibilities for monitoring activities & number of sites assigned to each monitor** *(Who will perform which activities? Consider monitor capacity – will one monitor be responsible for all or a certain number of sites?)*

- **Support departments to be visited (e.g. Pharmacy)** *(Which departments will be monitored and why? How will they be monitored and how often?)*

- **Data to be reviewed including Critical Data** *(How is the data collected and where is it recorded? Where is the Source data and how will it be accessed by the monitor? What monitoring activities will apply (e.g. Source Data Verification (SDV) or Source Data Review (SDR))? To what extent will it be checked (% of SDV required)? Critical data to be monitored (e.g. data relating to safety or study endpoints)? Critical data should be prioritised during monitoring & the monitoring plan should include details of what is considered critical data and how this should be treated.)*

- **Use of worksheets** *(A check for protocol compliance should be included in any monitoring activity to ensure that the procedures being followed are correct and in line with protocol requirements)*

- **IMP** *(Consider IMP accountability; shipment and delivery documentation; storage conditions including temperature monitoring; prescribers and prescribing)*

- **Considerations for unblinded monitors** *(Consider the use of unblinded monitors and how this will be managed; review of monitoring reports containing blinded information including who the appropriate reviewers will be; where monitoring reports containing unblinded information will be stored and what steps will be taken to ensure they are not shared inappropriately).*

- **Expectations regarding site team and PI availability during monitoring visits** *(What monitoring activities require site PI input? Is a meeting with the PI expected at every visit? How will PI oversight be monitored?)*

- **Oversight of the Investigator Site File, Documentation and Support Department records**

- **Review of safety information** *(How will identification and reporting of Serious Adverse Events be monitored? Consider the level of review of safety data that will be included. Does the protocol include any key safety assessments and how will these be monitored?)*

- **Escalation process (e.g. triggers for on-site monitoring; handling non-compliances; implementing CAPAs)** *(What is the criteria for escalation to more in-depth or frequent monitoring? What are the arrangements for management of unresolved issues, deviations and serious breaches of GCP and the protocol (including CAPAs)?)*

- **Management of actions arising from monitoring** *(Actions arising should be SMART (specific, measurable, achievable, realistic and time bound). The seriousness and area of the finding will influence the deadline and level of follow-up. Issues relating to safety reporting must be prioritised.)*

- **Supplies management**

- **Query management (e.g. data, protocol, IMP queries)**

- **Documentation of monitoring activities (e.g. monitoring logs, monitoring reports & self-assessment reports; responsibilities and timelines for preparing reports)** *(Consider the format and content of monitoring reports and review arrangements; timelines for the production of reports; documentation, reporting and management of non-compliances and deviations; management and follow up of actions arising with clear timelines.)*

- **Monitor training** (*How will they be trained and how will this be documented?)*

- **Site initiation and site training activities** *(Site initiation is a key monitoring activity which is conducted before the recruitment of participants. This is an opportunity to ensure that the relevant training has been provided to site staff and also that study documentation is in place and is correct. It may be useful to consider the ongoing*

training of sites and facilitation of good communication with sites and investigators when preparing the study monitoring plan).

(MHRA GCP Guide, 2012)

For high risk NuTH sponsored studies, a copy of the draft monitoring plan must be submitted to the RCT via tnu-tr.trialmonitoring@nhs.net for Sponsor review. Authorisation must be received by the RCT prior to initiation of the first study site. Monitoring activities should not take place until the monitoring plan has been fully authorised and all the required signatures are in place.

The monitoring plan must be reviewed on a regular basis and should be updated as required. The monitoring plan should be reviewed when a substantial amendment is made which results in a change to the objective, purpose, design, complexity, risk, blinding, size or endpoints of the study. Furthermore, given that monitoring methods should be targeted to the risks associated with the research, the monitoring plan should be reviewed in response to any relevant changes to the CTRAF.
The monitoring plan must include a version and date to ensure that the most current monitoring plan is being used. All versions must be stored within the Trial Master File (TMF) and Sponsor Oversight File (SOF) and obsolete versions marked as SUPERSEDED.

Any updates to the monitoring plan must be submitted to the RCT via tnu-tr.trialmonitoring@nhs.net
for Sponsor review and authorisation. The updated plan cannot be implemented until this authorisation has been issued by the RCT and the updated monitoring plan has been fully signed.

In exceptional circumstances (e.g. pandemics) a monitoring plan addendum may be appropriate to document temporary adaptations to monitoring procedures. These addendums must be reviewed and approved by sponsor prior to implementation.

Monitoring Plan Compliance

Full compliance with the monitoring plan is expected. Deviations from the plan must be documented and reported to the RCT (either in the relevant monitoring report or in a separate report or notification if applicable) in a timely manner. This documentation should include details of why the plan was not adhered to, any implications this has for the site or monitoring plan and any CAPAs that will be implemented to ensure that this is not repeated.

Persistent non-compliances with the monitoring plan may indicate either a training issue within the monitoring team or an issue with the achievability of the plan. The causes should be identified and addressed in a timely manner.

Monitor Qualifications and Training

All monitoring personnel must be appropriately trained, with adequate study, scientific and/or clinical knowledge as required.

The monitor must be familiar with the:

- Protocol;
- IMPs (if applicable);
- Devices (If applicable);
- Other Interventions (if applicable);
- Participant information sheet and consent form;
- Any other written information to be provided to subjects;
- Any relevant SOPs;
- GCP Guidelines; and
- All applicable regulatory requirements.

Training, qualifications and relevant experience of monitoring personnel must be clearly documented.

Types of Monitoring Activities

The methods of monitoring used and the extent of monitoring activities will be determined by the study type and risk rating allocated to the study. Various monitoring methods are described below, however monitoring is not limited to this list; any activity that provides oversight of a study may be considered a monitoring activity.

Investigator Site Selection

During study set up, the selection of investigator sites is usually delegated to the Chief Investigator (CI) and/or Trial Management Team via the Delegation of Duties Agreement (see 'Delegation of Sponsor Duties' SOP).

An assessment of the suitability of proposed sites must be conducted via completion of a site feasibility questionnaire/assessment that has been prepared taking in to account the specific aspects of the study.

Investigator sites may be selected based upon their previous knowledge/experience; specialism within the therapeutic area; previous experience within the IMP/product or due to recommendations from investigators or research networks.

The evaluation and selection of sites may include a site visit (e.g. if there is little knowledge about the site staff and/or if the trial requires complex equipment/assessments) or a remote assessment (e.g. if the site are known to the CI/trial management team and the trial has a simple design).

The method used to assess and select sites should be clearly documented in the TMF, along with the eventual decision on whether the site will be included (documentation should include the rationale as to why each site was deemed suitable for the study).

Further guidance can be found in regards to the site selection process via the NuTH SOP (DVL-PRC-GUIDE-005).

Site Initiation and Training

Once sites have been selected there may be an investigators meeting, where sites meet to be trained on the protocol, any associated equipment to be used, specific procedures and any data collection tools. This may take place via a face-to-face meeting or via teleconference.

In addition, there is usually a site initiation visit (SIV) where the monitor will meet with the site team to ensure they are adequately trained and ready to start the study.

The scope of these meetings will be determined by the type of study and associated risks identified in the Risk Assessment Documentation; for instance, a teleconference may be deemed appropriate if there is familiarity with the site or if the simplicity of the trial is such that on-site training is deemed unnecessary. Still, any such decisions should be clearly documented and justified in the Risk Assessment Documentation/monitoring plan and filed in the TMF.

For studies requiring regulatory green light (see NJRO-REG-SOP-005), the SIV report must be submitted to Sponsor for review alongside the request for green light.

Internal or Site Self-Monitoring

Once the trial has been initiated at sites, protocol compliance is often ensured through the Principal Investigator's (PIs) supervision at site and via appropriate monitoring as detailed within the monitoring plan.

This may include internal monitoring (which may also be referred to as site self-monitoring). This should be performed by members of the research team with responsibility for running the study. For low to medium risk studies that involve monitoring activities, this may be the only type of monitoring employed.

Internal monitoring tasks should include checks that (please note this is not an exhaustive list):

- All participants are consented on the most up to date, approved informed consent form and that all forms have been completed correctly.
- Data being collected is consistent with what is required by the study protocol.
- Where applicable Case Report Forms (CRF) or study worksheets are reviewed and authorised by members of the research team with responsibility to do so (as detailed within the protocol/study application);
- All adverse events have been recorded and reported appropriately.
- There are no gaps in the data. If gaps are found the study team must use their best endeavours to obtain this data and document this appropriately.

It also enables the site to provide data regarding recruitment and operational issues; for example, staff changes, key document amendments, deviations and non-compliances and a checklist of the Investigator Site File (ISF) contents.

For trials where internal (self) monitoring is incorporated into the monitoring plan, a copy of the internal monitoring template that sites will use to perform this task should be submitted to sponsor for review via tnu-tr.trialmonitoring@nhs.net.

All completed and signed forms should be filed in the ISF and TMF if held separately. They must also be sent to Sponsor for review via tnu-tr.trialmonitoring@nhs.net.

On-site Monitoring

On-site monitoring is undertaken through a physical visit to the study site by an appropriately trained study monitor. The degree and frequency of on-site monitoring will be informed by the CTRAF and detailed in the monitoring plan.

On-site visits enable a detailed review of the conduct of the study. Monitors can ensure this by discussing the study with the PI and site team to understand how the study is being conducted (e.g. whether safety reports are reviewed by an investigator; additional IMP storage areas; the process for source data collection/consent and who is doing what etc.). This also allows monitors to build a good working relationship with investigator sites.

The purposes of on-site monitoring include but are not limited to:

- The provision of study-specific training to site staff and assessment of their understanding of the protocol and trial procedures;
- Confirming that site staff have access to all required documents for the conduct of the trial;
- Review of informed consent to verify that this has been obtained and documented prior to participation, with only eligible subjects enrolled as per protocol;
- Ensuring that all required support departments are adequate;
- For CTIMPs and ATMPs, review of relevant documentation and storage conditions, ensuring supplies are sufficient;
- For device studies, review of relevant documentation and storage conditions, supplies (if applicable) are sufficient
- Source Data Verification (SDV) - comparing the data within the CRF or data capture document with the original source documentation and checking for transcription errors; and
- Source Data Review (SDR) - checking the quality of the source data, reviewing compliance with the protocol, ensuring appropriate delegation of duties and assessment of compliance with SOPs, GCP, etc.

A monitoring report should be produced to document the monitoring visit (including any findings and associated CAPAs); this must be submitted to Sponsor for review. The report and all associated correspondence should be saved in the TMF and ISF.

Central or Remote Monitoring

Central or remote monitoring is undertaken by monitors in a location remote from the study site and relies on the use and checking of data.

Statistical techniques can be employed to identify unusual patterns of data, and can be used to detect sites with apparent deviations from the protocol.

Examples of central/remote monitoring techniques include:

- **A remote review of consent** (e.g. correct version used; authorised delegated person taking consent; signed and dated by subject; assent (as required) etc.)
- **Remote review of Investigator Site File** (e.g. Delegation logs; research team's CV/GCP/training etc. This may be done using self-completed checklists.
- **Remote training** (e.g. teleconference/training packs)
- **Statistical techniques to identify patterns and trends** (which may highlight invalid data; incorrect procedures; fraud; implausible data;
- Identify outliers or unusual variability; changes within normal limits for lab values etc. This may also involve assessing the rates of reporting – e.g. number of adverse events or missing data between sites).
- **Remote CRF/data review** (such as performance indicators – e.g. late entry of data; CRF completion; missing data; calendar checks for visit dates and date of consent/randomisation; recruitment; subject eligibility and protocol compliance; routine data surveillance; sample processing forms and assessment of participant demographics – e.g. identifying patterns at a site which may be indicative of repeated inclusion of a participant or copying of the data).
- **Remote SDV** (to be conducted as per site local policies. Please refer to DLV-GEN-SOP-002 for remote monitoring processes at NUTH).

Central monitoring checks should be documented and all relevant documentation and correspondence held in the Trial Master File (TMF).

Triggered Monitoring

Issues or concerns raised through central monitoring may trigger a more in-depth assessment of a site (e.g. via a triggered on-site visit) or the need to review the risk and potentially revise the monitoring plan.

Triggers may include: protocol non-compliances; data non-compliances; notably high or low serious adverse event rates; lower or higher than expected recruitment; IMP management issues or non-compliance with the applicable regulations/SOPs.

A risk based, targeted monitoring strategy helps to ensure that sites requiring additional support in response to compliance issues are identified.

Any triggered monitoring visits must be documented in a monitoring report and sent to Sponsor for review. For high risk, NuTH sponsored studies falling under the RCT, all reports should be submitted to: tnu-tr.trialmonitoring@nhs.net. For low to medium risk studies, these should be submitted to the RGT for review using: nuth.genericqueries@nhs.net.

The reports and all associated correspondence should be saved in the TMF and ISF.

Close Out Activities

Once a trial has been completed or a site closed prematurely it is important to ensure the investigator has a complete and independent record of the trial at their site and that this will be stored securely for the required archiving period under control of the investigator.

Close out activities should be completed prior to archiving and can be achieved via an onsite visit (which may include a review of the documentation and archiving facilities) or centrally (via discussion and documentation e.g. using questionnaires/checklists completed by the site).

If sites are non-responsive to the close out request, the trial manager or should notify the sponsor team to agree further action.

Co-Monitoring

In certain circumstances where the responsibility for monitoring is delegated to a trial management team, the Sponsor may wish to carry out co-monitoring.

Co-monitoring visits are monitoring visits performed by both a study monitor and an appropriately trained member of the Sponsor team. The purpose of co-monitoring is to evaluate whether study monitors are effectively carrying out visit activities in compliance with the study monitoring plan.

Co-monitoring visits may be conducted randomly or may be undertaken in response to occurrences during the study, including but not limited to protocol/GCP non-compliances.

The NuTH co-monitoring template can be accessed via the following link.

All co-monitoring personnel must be appropriately trained and should be familiar with the:

- Protocol;
- IMPs (if applicable);
- Devices (if applicable);
- Other Interventions (if applicable);
- Participant information sheet and consent form;
- Any other written information to be provided to subjects;
- Any relevant SOPs;
- GCP Guidelines; and
- All applicable regulatory requirements.

Training and qualifications of co-monitoring personnel should be retained within personal training files.

Considerations for Blinded Monitoring

There are additional considerations for the monitoring of blinded studies and a separate, unblinded monitor should be considered, particularly for double blinded studies.

Where the monitoring plan incorporates unblinded monitoring, the Trial Manager should remain blinded to reduce the potential for bias and accidental unblinding of site personnel. However, a second unblinded monitor should conduct the monitoring of the intervention/administration.

The unblinded monitor should also review the documentation to verify that the blind has been maintained. Documentation that will help with this assessment include IMP or ATMP preparation logs; IMP/ATMP/medical device administration logs; site delegation logs and delegated tasks; and training logs relating to maintaining the blind.

Consideration must also be given to the storage of documents relating to blinded aspects of the study within the TMF to ensure that blinded study personnel do not access them and inadvertently unblind themselves. Mitigations to prevent these risks should be documented in the CTRAF and details relating to unblinded monitoring reporting (and storage) must be included in the monitoring plan.

Unblinded monitoring reports must be sent to the NJRO Quality Assurance (QA) Manager or Assistant QA manager for review (contact details can be found on the NJRO website). Unblinded reports must **not** be sent to the RCT as this ensures that Sponsor representatives from the RCT remain blinded. This is important given their attendance at Trial Management Group meetings, as it reduces the potential for bias and accidental unblinding of the CI and central study management team.

Unblinded monitoring information relating to pharmacy aspects of the study (e.g. IMP storage, distribution, prescribing etc.) must also be sent to the unblinded pharmacy management team within NuTH via pharmacyrandd@nhs.net via default, unless certain members of the Sponsor Pharmacy team are also blinded. If this is the case, alternative contact details will be clarified in the Pharmacy Manual and/or Protocol and should also feature within the Monitoring Plan.

Following their review of an unblinded monitoring report, the QA and NuTH Pharmacy personnel must ensure that feedback is only sent to the relevant unblinded site staff for actioning where appropriate. This is to avoid any accidental unblinding.

Sponsor review of Monitoring Reports

All monitoring reports must be submitted in a timely manner to Sponsor for review via: tnu-tr.trialmonitoring@nhs.net.

Once received e-mail confirmation of receipt will be sent and the monitoring report logged for review by an appropriately delegated member of the RCT. Following review confirmation will be sent to the Trial Management Team including any actions or risks identified. If changes to the risk assessment are required the continuous risk assessment form will be completed (see NJRO-REG-SOP-004). A copy of the fully executed monitoring report will be returned (where required) when all CAPAs are deemed appropriate.

7. References

ICH GCP Guidelines with Integrated Addendum E6 (R2) Step 4, November 2016.
MHRA Good Clinical Practice Guide, 2012.

8. Appendices

NA