University of East Anglia

Our Vision
The best care for every patient

NHS
Norfolk and Norwich University Hospitals
NHS Foundation Trust

SOP 330 Monitoring Clinical Trials of an Investigational Medicinal Product and Device Trials Sponsored by NNUH

For Use in:	Research & Development
By:	All staff
For:	All staff involved in the conduct of research
Division responsible for document:	Research & Development
Key words:	Monitoring
Name of document author:	Basia Brown
Job title of document author:	Research Governance Coordinator
Name of document author's Line Manager:	Julie Dawson
Job title of author's Line Manager:	Research Services Manager
Supported by:	Julie Dawson NNUH Sarah Ruthven UEA
Assessed and approved by:	Julie Dawson: Research Services Manager NNUH Sarah Ruthven: Research Manager UEA
Date of approval:	13 June 2023
To be reviewed before: This document remains current after this date but will be under review	13 June 2026 (3 years, unless legislation or process changes)
Reference and / or Trust Docs ID No:	13485
Version No:	2
Description of changes:	Updated to include guidance on an escalation process for Actions that are repeatedly not addressed.

This Standard Operating Procedure (SOP) is available on the Research & Development pages on the NNUH website

Copies printed from the website are only valid on the day of printing.

SOP 330 Monitoring Clinical Trials of an Investigational Medicinal Product and Device Trials Sponsored by NNUH

1. Contents

2. Definitions of Terms Used / Glossary

Central or Remote monitoring	Monitoring activities undertaken by the monitoring personnel in a location remote from the investigator site (for example, a data centre).
CI	Chief Investigator
CRF	Case Report Form
CTIMP	Clinical Trial of an Investigational Medicinal Product
GCP	Good Clinical Practice
Likelihood	The state or fact of something being likely. Probability.
Monitoring Plan	A description of the methods, responsibilities and requirements for monitoring the trial, according to the Integrated Addendum in GCP E6 (R2)
Monitoring Report	A written report from the monitor to the sponsor after each site visit.
NCTU	Norwich Clinical Trials Unit
NNUH	Norfolk and Norwich University Hospital
On site Monitoring	Monitoring activities primarily undertaken during a physical visit to the investigator site by one or more monitoring personnel
PI	Principal Investigator
QC	Quality Control

R&D	Research and Development
SDV	Source Data Verification: An important part of monitoring is to compare the entries in case report forms (CRFs) with the original source documents (e.g. patient notes, test results).
SIV	Site Initiation Visit
SOP	Standard Operating Procedure
TMF	Trial Master File
UEA	University of East Anglia

3. Scope

This SOP describes the process and responsibilities for the monitoring of Clinical Trials of an Investigational Medicinal Product (CTIMPs) and Medical Device Trials **Sponsored by the Norfolk and Norwich University Hospitals NHS Foundation Trust**

4. Purpose

Monitoring is an integral process in the Quality Control (QC) of a trial. Monitoring ensures that a trial it is conducted, recorded, and reported in accordance with the trial protocol, applicable SOPs, policies, GCP / ISO 14155, and the applicable regulatory requirement(s)

The purpose of trial monitoring is to verify that:

- The rights and well–being of human subjects are protected.
- The reported trial data are accurate, complete and verifiable from source documents.
- The conduct of the trial is in compliance with the currently approved protocol/amendment(s), with GCP, and with the applicable regulatory requirement(s).

For oversight of NNUH Sponsored studies that are not classified as CTIMPs or Device Trials refer to WPD 022 Sponsor Oversight (non CTIMPs and non-Device Trials)

5. Responsibilities

Sponsor
• Overall management of trial • Selection of monitoring personnel • Ensure that the monitor is appropriately qualified and trained to monitor the trial adequately • Determine the extent and nature of monitoring required based on review of the risk assessment for the study. • Approve the trial specific risk adapted monitoring plan

Monitor
• Ensure a trial specific monitoring plan is developed proportionate to the requirements of the study and its level of risk • Comply with the monitoring plan, and ensure that any changes to the plan have prior approval of the Sponsor. • Conduct monitoring visit and provide reports to the Sponsor. **For further information for NNUH Monitors refer to the Working Process Document WPD010 Monitors Guide to the Monitoring of Clinical Trials of an Investigational Medicinal Product and Device Trials.**

Chief Investigator / Principal Investigator
• Review and agree the monitoring plan • Facilitate monitoring access for the study • Ensure that all essential documents/source data/ participant information is available for monitoring visits • Act on any issues identified in the monitoring reports in a timely manner • Respond to monitor requests for completion/correction of data • Co-ordinate trial management to facilitate central, remote and/or site monitoring

6. Procedure for studies monitored by NCTU

For NNUH sponsored studies where the Norwich Clinical Trials Unit (NCTU) has been delegated the responsibility of study monitoring, NCTU monitoring/working instructions and documentation will apply.

7. Qualifications of a Monitor

Monitors should be appropriately trained, have working knowledge of regulatory requirements and have the sufficient scientific and/or clinical knowledge to allow them to monitor the trial adequately. A monitor's qualifications should be documented. Training records, including relevant qualifications, should be kept by the monitor. Please refer to SOP 505 "Training requirement, creating and maintaining training records" for further details.

8. Process

a. Risk based approach

NNUH adopts a risk based approached for monitoring of clinical trials, allowing focus on preventing and mitigating important and likely risks to data quality and integrity, protection of participants rights and trial integrity.

A risk assessment will be completed to guide decision on the type, frequency and extend of monitoring required for the study. The extent of monitoring is not a standardised activity as it depends on the level of risk and the nature of the trial. It can also vary thought the

duration of the study. There are different types of monitoring and a combination of these may be used depending on risks associated with a particular study **A minimum requirement for monitoring of NNUH Sponsored studies is indicated in Appendix 1.**

Please refer to SOP 720 Risk Assessment of Clinical Trials Sponsored by the NNUH and UEA for further details.

b. Monitoring plan

Based on the Risk Assessment a Monitoring Plan will be put in place by the Sponsor's personnel or delegate with responsibilities for monitoring of the trial.

- The plan should describe the monitoring strategy aimed at mitigating identified risk, in particular:
  - type of monitoring
  - frequency of monitoring.
  - Data to be reviewed – the amount of source data verification required.
  - what documents / information will be requested for review and how often
  - expectations for availability of investigator during monitoring visit
  - expectations for self-monitoring checks completed by sites
  - list of triggers or thresholds of acceptability which will warrant triggered monitoring activities
  - Any supporting departments that will be visited (e.g. pharmacy, laboratory)
  - Escalation process
  - Timelines for preparing and reviewing of monitoring reports.
  - If monitoring activities are shared

- Monitoring plan must be finalised prior to commencement of recruitment. The plan must be approved by the Sponsor and agreed by CI.

- Any changes to monitoring plan must be approved by the Sponsor prior to implementing changes.

- The monitoring plan should be reviewed when circumstance arise leading to review of original risk assessment for example a substantial amendment is made, if there are any concerns regarding GCP compliance or any change in research staff that may affect the original risk assessment of the study. These changes may result in an increase in monitoring activities or change in type of monitoring.

c. Type of monitoring

i. Centralised monitoring

This monitoring approach focuses on collection of data and documents from site(s) in the centralised, remote location where it is being analysed by sponsor or delegated representative.

The value of central monitoring is real time identification of risks, unusual patterns, issues with consistency, deviations or issues around completion of CRFs.

Although omissions such as failure to report a serious adverse event (SAE) or data entry errors cannot be detected directly via central monitoring, it may be possible to compare data from the different sites to identify sites that warrant investigation.

When reviewing, it is important to recognise that some variability is to be expected. Data that is “too good” should raise suspicion in the same way as data that is unusually poor.

Where centralised monitoring indicates problems, it can be used to efficiently direct on-site monitoring activities to those sites requiring further investigation and/or additional training support.

ii. On site monitoring

On-site monitoring visits may be used in a variety of different ways:

- to educate staff about the trial; review understanding of the protocol and trial procedures;
- to verify that the staff at the site have access to the necessary documents to conduct the trial;
- to ensure that the required pharmacy and laboratory resources are adequate;
- to check adherence to the protocol and GCP by reviewing such things as signed consent forms and patient eligibility,
- to verify all protocol required data (e.g. adverse event/concomitant medication) have been recorded on the CRFs and compared with data in the clinical records (source data) to identify errors of omission as well as inaccuracies.
- To check trial procedures (e.g. informed consent procedures, data collection, CRF completion) to ensure quality and consistency and confirm all assessments are being made by appropriately qualified staff;
- Division of monitoring activities if these are conducted by more than one Sponsor delegate.

d. Frequency of monitoring

Monitoring activities should occur before the study starts (SIV) during the study (routine monitoring) and at study completion (close down visit).

The frequency and intensity of monitoring depends on study parameters and should be proportionate to risk identified in risk assessment.

A site initiation visit (SIV) for each research site should take place before recruitment begins at the site to ensure that all essential study documents are in place and research staff have been trained in study procedures before the study starts.

Please refer to SOP 410 Set up and Initiation of an Investigator Site for details.

If, during the course of a study circumstances arise which suggest persistent noncompliance with the protocol or/and regulatory requirements or when identified issue require further investigation additional monitoring activities will be triggered.

9. Monitoring Visits

a. Preparing for a Monitoring Visit

- The monitor will inform the research team where, when and for how long the visit will take place
- Monitor will indicate which documents and patient records should be available during the visit for review.
- The monitor will inform the CI and PI of the schedule of monitoring visits and indicate expectation of investigator's availability during the visit
- The monitor will arrange with the research team for a room/desk to be available for the visit
- If other departments (e.g. pharmacy) are to be visited they should be informed and arrangements made to review the files and or equipment & facilities

b. During a Monitoring Visit

- A member of the research team should be available during the visit to ensure that all queries can be addressed in real time
- The monitor will usually require a review of the requested documents and then arrange to meet with the CI/PI or a delegated member of the research team to discuss the summary of findings (when applicable)
- The Monitor will follow up on the monitoring plan and follow up on the outstanding actions with the research team, and sign the Monitoring Visit Log.

c. Following the Monitoring Visit

- Research team to ensure all source documents are returned to the respective departments
- Monitor to complete the monitoring visit report, summarise what has been reviewed and state significant findings and discrepancies. Include any recommendations for corrective and preventative actions
- Monitor to send the report to the Sponsor and CI/PI within timelines set in Monitoring Plan

- Monitoring report should be filed in the TMF, and the sponsors electronic study folder
- The CI/PI should ensure that all outstanding actions are addressed promptly (as per Monitoring Plan), and prior to the next visit, unless a specific time for implementation is required or agreed
- Communication should continue between monitor and study team between visits when necessary to follow up outstanding action items

10. Monitoring Report

Following a monitoring visit or a period of central monitoring, the monitor must provide the Sponsor as well as Investigator or supporting department with a copy of monitoring report, which should include:

- Date, site and name of Monitor
- Name of the research staff present during monitoring visit.
- Details of documents reviewed
- Details of actions / checks undertaken by Monitor (e.g. check of samples present, storage location of IMP)
- significant findings, deviations (if applicable), deficiencies, actions taken or recommended.

11. Non-compliance and Escalation process

It is the responsibility of the Investigator to engage with the Monitor and respond to any actions and non-compliances identified via monitoring activities in a timely and proactive manner.

Any non-compliance should be addressed, reported, and recorded in line with SOP 210 Breach to GCP or Protocol.

If any actions or non-compliance are not resolved satisfactory or in a timely manner the Research Services Manager and Research Governance Coordinator will be informed of the concerns and a meeting between the Investigator, Monitor and Research Governance Co-ordinator will be organised with the aim of addressing any issues.

If actions are still not resolved the Research Governance Coordinator will escalate these to Joint Research Governance Committee for action.

12. Closure of the study

Following notification to the Sponsor of last patient last visit, all the data have been collected (there are no more outstanding AEs/SAEs & all outstanding Queries/data clarification forms have been resolved appropriately), the database is locked and ready for statistical analysis, and the study conduct has ended, the Monitor should arrange a final close-down visit. This is to ensure that all essential documents at site are complete and reconciled, any outstanding follow-up or corrective actions are completed by the study

team, that drug accountability and or equipment accountability (when applicable) is complete and to ensure that data is prepared for archiving.

Site close-down visits are mandatory and it is the responsibility of the CI to ensure that these occur for sites that have been activated (i.e. site initiation took place). A close-down report will be completed by the Monitor after the visit and a copy of this will be filed in the TMF and investigator site file.

In the event of site close down resulting from early study termination, refer to **SOP 335 Research Project Closure (Including procedure or Project suspension or early termination)** for more information.

13. References and Related Documents

References	
ICH GCP E6 / SI 2004/1041	
SOP No.	**SOP Title**
SOP 210	Breach to GCP or Protocol
SOP 335	Research Project Closure
SOP 505	Training requirement, creating and maintaining training records
SOP 720	Risk Assessment of Clinical Trials Sponsored by the NNUH and UEA

14. Approval

Author	Basia Brown
Role	Research Governance Coordinator
Approved & Authorised NNUH	Julie Dawson
Role	Research Services Manager
Signature	DocuSigned by: Julie Dawson 4CBAB366CF354A2...
Date	13 June 2023 | 11:11 BST
Approved & Authorised UEA	Sarah Ruthven
Role	Research Manager
Signature	DocuSigned by: Sarah Ruthven 6EB42B4E497249C...
Date	21 June 2023 | 9:55 BST

15. Reason for new version and Training Implication

This SOP replaces the previous version number V1.5

Changes made	
Reason	• New layout • Revision in procedure • Change requests raised post MHRA inspection
Training Implication	**Yes**
Actions required	• Additional training may be required

Appendix 1 a minimum requirement for monitoring of NNUH Sponsored studies

			Concerns identified in the assessment of risk associated with the design, methods, or conduct of the study (other than intervention), **which remain after mitigations are in place**	
			NO	**YES**
Risk associated with Intervention	**CTIMPS**	**Devices**		
	Type A - risk not higher than the risk of standard medical care	**Class I**	**Low intensity** Central monitoring / oversight of protocol adherence and data quality. No requirement of site visiting unless there are concerns	**Low +** As outlined in “low intensity”, plus appropriate monitoring to address the specific vulnerabilities associated with trial design, methods or conduct identified in the risk assessment.
	Type B - risk somewhat higher than the risk of standard medical care	**Class II A & B**	**Moderate intensity** Central monitoring / oversight of safety data quality and timeliness as well as protocol adherence and quality of other trial data. Triggered visits for poor data return or protocol adherence concerns as well as unusually low or high frequency of Serious Adverse Events (SAE) reports (for studies where between-site comparisons are possible)	**Moderate+** As outlined in “moderate intensity”, plus appropriate monitoring appropriate monitoring to address the specific vulnerabilities associated with trial design, methods or conduct identified in the risk assessment
	Type c - risk markedly higher than the risk of standard medical care	**Class III**	**Higher intensity** More intense monitoring / oversight than above to have confidence in the completeness and reliability of safety data	**Higher+** As outlined in “higher intensity”, plus appropriate monitoring to address the specific vulnerabilities associated with trial design, methods or conduct identified in the risk assessment.