Portsmouth Hospitals NHS
NHS Trust

Standard Operating Procedure (SOP) for Developing a Monitoring Plan for Studies Sponsored by PHT

For Completion by SOP Author	
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If you are reading this SOP in printed form then you are reading an uncontrolled document. You must therefore verify that the version number and date given below are the most recent, by cross-checking with the Trust research website before proceeding with implementation.

Portsmouth Hospitals NHS Trust is committed to ensuring that, as far as is reasonably practicable, the way we provide services to the public and the way we treat our staff reflects their individual needs and does not discriminate against individuals or groups on any grounds. This SOP has been assessed accordingly

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1. INTRODUCTION

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

A general approach to monitoring may be outlined in the study protocol. The specific details of the monitoring activities to be conducted will then be documented within the separate monitoring plan.

A monitoring plan will be informed by the study risk assessment which will contain details of the study risks and any actions to mitigate these. Any residual risks may require monitoring. As such the requirement for a monitoring plan will be based on the outcome of the risk assessment.

Most monitoring plans will contain, as a minimum:

- Verification of the existence of participants
- Checks for valid, informed consent
- Checks relating to safety and safety reporting
- Checks of data quality and completeness
- Checks of compliance with relevant regulation, legislation, the study protocol and Sponsor SOPs

The methods used and the extent of these checks will vary considerably depending on the study type.

2. PURPOSE

The purpose of this document is to describe the SOP for developing and maintaining a study specific monitoring plan and for obtaining Sponsor authorisation for that plan. This includes:

- Producing an initial monitoring plan based on the initial study risk assessment.
- Reviewing and making updates to the monitoring plan in line with any updates to the risk assessment and ongoing evaluation based on findings from monitoring and other oversight activities.

3. SCOPE

This SOP relates to all studies sponsored by Portsmouth Hospitals NHS Trust (PHT) that have not had monitoring functions delegated to an external organization.

It is anticipated that monitoring plan development and monitoring activities for studies with monitoring delegated to an external organisation will follow their relevant SOPs and be outlined in the roles and responsibilities.

The Trust recognises that some external sponsors, networks, funders and employers may require the use of their own SOPs for the good governance of research. In such cases it is the responsibility of the Portsmouth Hospitals Trust user (including those individuals contracted to work on behalf of the Trust), to ensure that the external SOP is compatible with the procedure outlined below. If the external SOP contradicts the Trust's procedure then approval must be sought in writing from the Research and Quality Manager.

In the event of an infection outbreak, flu pandemic or major incident, the Trust recognizes that it may not be possible to adhere to all aspects of this document. In such circumstances, staff should take advice from their manager and all possible action must be taken to maintain ongoing patient and staff safety

4. ABBREVIATIONS & DEFINITIONS

Abbreviation	Meaning
CI	Chief Investigator
eCRF/CRF	electronic Case Report Form
CTIMP	Clinical Trial of Investigational Medicinal Product
DMC	Data Monitoring Committee
DSMB	Data Safety Monitoring Boards
GCP	Good Clinical Practice
MHRA	Medicines and Health products Regulatory Agency
PHT	Portsmouth Hospitals NHS Trust
PI	Principal Investigator
RF	Research Facilitator
RGG	Research Governance Group
R&I	Research & Innovation (Office)
SAE	Serious Adverse Event
SOP	Standard Operating Procedure
TMF	Trial Master File
TSC	Trial Steering Committee

Term	Definition
PHT Sponsored Studies	Studies which Portsmouth Hospitals NHS Trust have ultimate responsibility for the initiation, management of and financing for. They take primary responsibility for ensuring that the design of the study meets appropriate standards and that arrangements are in place to ensure appropriate conduct and reporting.
Study Team	The people involved in the conduct of a research project. There may be different research teams for the project at different sites.

5. DUTIES AND RESPONSIBILITIES

Role	Responsibilities
Sponsor	• The R&I office will facilitate the completion of the monitoring plan by working closely with the Chief Investigator and their Study Team • Review and update the monitoring plan as required
Chief Investigator (CI) & Study Team	• Work with the R&I office to complete the monitoring plan and where necessary involve other staff with expertise in different fields. • CI will have primary responsibility for ensuring the monitoring plan is adhered to (this will be supported, where applicable, by the RF) • Review and update the monitoring plan as required

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6. PROCESS

6.1 Monitoring Plan Template

Monitoring plans should be written using the monitoring plan template (refer to section 8). The template is designed to be adapted depending on the type of study and it's identified risks.

6.2 Monitoring Strategies

It is recommended to take a proportionate and risk based approach to the management and monitoring of the study. Monitoring activities should be focused on aspects of the study that affect patient safety and critical data items.

Monitoring methods will be influenced by any regulatory or legislative requirements, ensuring compliance with the study protocol, GCP, local policies and SOPs. Examples of monitoring methods can be found in appendix 1

Risk based adaptations can be incorporated to build flexibility into the monitoring strategy. For example, the monitoring activities at the start of a study may be of high intensity and then decrease as the study progresses and compliance is evidenced. If the study is multi site then consider high intensity monitoring for sites unknown to the sponsor or that are inexperienced, and lower intensity monitoring for sites that have been used in past studies and have a good reputation for compliance.

Consider resource availability (including personnel and financial) when preparing the monitoring plan. It is essential that the monitoring activities outlined in the monitoring plan are achievable and can be maintained throughout the study.

6.3 Content of a Monitoring Plan

Monitoring method, frequency, focus and intensity (i.e. how much of a potential item will be reviewed), will be based on factors identified in the risk assessment and any proposed mitigation strategies. A guide to the focus and intensity of monitoring can be found in appendix 2.

The following should be included in all monitoring plans:

Item	Considerations
Monitoring methods to be used and the rationale for their selection	• Will on-site, central or a mixture of monitoring methods be used? • Why have these been chosen? • See appendix 1 for examples of monitoring methods
Details of which sites will be monitored (if multisite)	• Will all sites be monitored or just a selection? • If a selection, how/why/when will they be monitored?
The frequency and timing of monitoring activities	• When will monitoring occur? • Will it be scheduled for a particular time point or will it be triggered?

Details of standards and/or SOPs to be followed when monitoring	• Which standards or regulations will be monitored against? • Are there specific SOPs or procedures to be followed?
Data to be reviewed during monitoring	• How is this 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 or source data validation? • To what extent will it be checked (a certain percentage or all)?
Details of any ancillary departments (e.g. pharmacy, labs or imaging) to be monitored	• Which departments will be monitored and why? • How will they be monitored and how often?
PI engagement in monitoring activities	• What monitoring activities require input of the site PI? • Is a meeting with the PI expected at every monitoring visit? • How will PI oversight be monitored?
Responsibilities for monitoring activities	• Who will perform which activities? • How will they be trained and how will this be documented? • Monitor capacity (will one monitor be responsible for all or a certain number of sites)?
Oversight of documentation and site files	• Including review of investigator site files and study documentation at site
Review of safety information	• How will identification and reporting of SAEs be monitored? • Does the protocol include any key safety assessments- how will these be monitored?
Documentation of monitoring activities	• The format of monitoring reports and review arrangements • Timelines for the production of reports • Documentation and management of monitoring findings
A clearly defined escalation process following identification of issues	• What is the criteria for escalation to more in-depth or frequent monitoring? • What are arrangements for management of unresolved issues, deviations and serious breaches of GCP and the protocol (including corrective and preventative actions)?
Additional items that should be considered when developing a monitoring plan are:	
Critical Data	• Data relating to safety or to study endpoints is often referred to as critical data and should be prioritised during monitoring • The monitoring plan must include details of what is considered to be critical data and how this should be treated
DEVICE, CTIMP and ATIMP Studies	• IMP accountability • Device usage accountability

Blinded Studies	• The use of unblinded monitors and how this will be managed • Review of monitoring reports containing unblinded information including who 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
Use of Worksheets/Crib sheets (i.e. to record study assessments or in laboratories)	• A check for compliance with the protocol should be included in any monitoring activity to ensure that the procedures being followed are correct and in line with protocol requirements
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.

6.4 Monitoring Plan Implementation

Ensure all parties that are involved in the monitoring of the study have reviewed and agreed the proposed monitoring plan. This could include the Trial Manager, CI/PI, Research nurses, the Pharmacy team, Data Manager and the Statistician.

The study monitoring plan should be completed and authorised prior to the initiation of the first study site. Authorisation will take the form of the signature of the Sponsor representative (the Chair of RGG) and the CI on the monitoring plan cover page.

A signed copy will be saved in the TMF and the study folder on the R&I G-drive

All updates to a monitoring plan must be reviewed and authorised by the Sponsor representative and CI.

The monitoring plan and any updates will be added to the monitoring tracker by the R&I office. This tracker is reviewed regularly to maintain oversight.

6.5 Trial Oversight Committees (Data Monitoring and Trial Steering Committees)

Monitoring of accumulating data and supervision of a study, as performed by Trial Oversight Committees such as a Data Monitoring Committee (DMC) and Trial Steering Committee (TSC), are classed as monitoring activities. The need to establish these committees, (or not), for a particular study will be identified during the study risk assessment.

It is recommended, that for studies where trial oversight committees are established, the monitoring plan details this.

Information on the remit, meeting frequency and output of such committee will be documented in the relevant committee terms of reference or the study protocol rather than in the study monitoring plan.

6.6 Compliance with Monitoring Plans

Full compliance with a monitoring plan is expected. Deviations from the plan should be documented and reported in accordance with the SOP for Reporting and Managing Non-Compliance and Serious Breaches in Clinical Research (PHT/RDSOP/002). 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 corrective actions that will be put in place 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.

The monitoring plan should be reviewed on a regular basis (at time intervals agreed and documented within it) and should be updated as required including when the study risk assessment is updated.

7. TRAINING REQUIREMENTS

R&I Office staff designing the monitoring for PHT sponsored studies must be trained in this SOP.

It is advised that Chief Investigators and delegated members of their Study Team based at the lead site/coordinating centre for any PHT Sponsored Studies read this SOP. Training is not essential

"The Research Dept., will endeavour to notify staff of SOP developments that may be relevant to them. SOPs are available on the Research department website. Updates on SOPs will feature in Research newsletters and communications and disseminate at local research meetings. It is the responsibility of all research active staff to ensure that they read the issued updates that may be relevant to them.

When a new SOP is authorised, or when an existing SOP is revised, self directed training must be carried out by all staff to which the SOP is relevant and this training documented in their training record. A template is provided to support this process. A study specific SOP training plan will be developed for investigators on high risk PHT Sponsored studies.

Staff should take time to read and fully understand the SOP and relevant documents, ensuring that they are able to implement the SOP when required. If clarification is needed then the trainee should approach their line manager and the SOP Controller who will arrange additional training. All staff should complete their training prior to the published implementation date which will normally be between 2-6 weeks after publication.

All staff are responsible for maintaining their own SOP Training Records and copies must be made available to line managers, the SOP Controller or study monitors on request."

8. REFERENCES AND ASSOCIATED DOCUMENTATION

Associated documents:

- Template – Monitoring Plan
- Monitoring Tracker 2019
- SOP for Reporting and Managing Non-Compliance and Serious Breaches in Clinical Research (PHT/RDSOP/002)

Reference:

- The MHRA Good Clinical Practice Guide 2012
- MHRA FAQs, 22nd February 2013
- MRC/DH Joint Project to codify good practice in publicly-funded UK clinical trials with medicines. Work stream 4: Trial Management and Monitoring: C) Monitoring Procedures, June 2017
- ICH Guideline for GCP E6 (R2), Step 4, 9th November 2016
- The Newcastle upon Tyne Hospitals NHS Foundation Trust & Newcastle University: SOP-JRO-27-001 Developing and Maintaining a Monitoring Plan
- Risk Assessment and Risk-based Management and Monitoring Workshop, UKTMN Annual Conference, 10th October 2017
- https://www.invo.org.uk

9. VERSION HISTORY LOG

This area should detail the version history for this document. It should detail the key elements of the changes to the versions.

Version	Date Implemented	Details of Significant Changes
1.0	16 Jan 2020	New document

10. APPENDICES

10.1 Appendix 1. Guidance on the different types of monitoring

Types of monitoring:

A. Site Selection and Site Initiation Visits

The selection process of a host site may vary for example the considerations will differ if a site is already known to the sponsor or if the site is known through its reputation as an expert in a particular therapeutic area. The rationale for the decision to select a site should be recorded as evidence the site is suitable for the study.

A site initiation visit is an opportunity to ensure the site is ready to start, that all the documentation is correct, the staff are trained in the study procedures and equipment. The SIV can be face-to face or via teleconference or videoconference.

B. On-site Monitoring

This is monitoring that takes place during a physical visit to the site. It can often be the most convenient in single site studies and is excellent for building relations with the study team giving the opportunity to offer training and to view facilities. On-site monitoring also allows the opportunity to verify participants exist, to review medical records for unreported SAEs and conduct source data verification.

On-site monitoring can be resource intensive and can carry a travel burden when visiting host sites. It is therefore recommended central monitoring be considered where possible. Could the R&D office of the host site conduct the monitoring? Can on-site monitoring be reduced or targeted?

Example areas covered by On-site monitoring

- Consent process – verifies participants exist and consent has been given in accordance with GCP
- Review of medical notes – confirms protocol compliance and checks for unreported adverse events
- Source data – checks on outcome data to demonstrate accuracy and reliability of results.
- Safety reporting – confirm correct procedures have been followed to protect the participant
- Trial Master File – check the correct study documentation is in place, the appropriate approvals have been received and patients documents are up to date.
- Delegation of duties – checks research staff are appropriately trained and delegated
- Facilities and equipment – ensure suitability for the study
- IMP management – check IMP has been handled appropriately
- Device Accountability – check device has been issued appropriately

C. Central Monitoring

This is monitoring that takes place in a location remote from the investigator site. It can offer insights into the study that sometimes can't be visible from on-site monitoring. E.g. reports from databases and statistical analysis can identify non compliances when compared across sites.

One site could be significantly different from other sites for example in SAE metrics, identifying the site as an outlier. It is less resource intensive than on-site monitoring and does not have the same travel burden.

Examples of Central Monitoring

- Remote review of Consent forms
- Laboratory reports
- Questionnaires and contents checklists can be completed by the investigator site to check compliance and contents of the site file
- Remote review of the data on the CRFs, IMP/Device accountability records, safety data and other operational data to confirm protocol compliance
- Review of training and delegation of duties (CVs, GCP records and delegation logs)
- Statistical analysis to identify patterns and trends and spot site outliers

D. Statistical Monitoring

Statistical monitoring is an aspect of central monitoring. It is where the accumulating data such as clinical data from the CRF (e.g. SAE event rates) or performance data (e.g. number of data queries) are examined using statistical approaches or modelling across the study.

This method allows for trending and modelling with the aim of identifying any unusual patterns/variances within the data, and in particular if any sites appear to be 'outliers'.

E. Data Monitoring Committees (DMC) / Data Safety Monitoring Boards (DSMB)

A DMC/DSMB is a group of experts that may be put in place to review accumulating data from ongoing trials and to advise the TSC or study team of any important information (e.g. safety issues) and the continuation of the study (whether there is any reason to stop the study).

F. Trial Management Group (TMG) / Trial Steering Committees (TSC)

The TMG normally includes those individuals responsible for the day-to-day management of the trial, such as the Chief Investigator, statistician, trial manager, research nurse, data manager. The role of the group is to monitor all aspects of the conduct and progress of the trial, ensure that the protocol is adhered to and take appropriate action to safeguard participants and the quality of the trial itself.

The role of the Trial Steering Committee (TSC) is to provide the overall supervision of the trial. Ideally, the TSC should include members who are independent of the investigators, their employing organisations, funders and sponsors. The TSC should monitor trial progress and conduct and advise on scientific credibility. The TSC will consider and act, as appropriate, upon the recommendations of the Data Monitoring Committee (DMC) or equivalent. The need for a TSC will depend on the complexity of the study and will be identified by the risk assessment.

G. Close Out Monitoring

When a study comes to a close checks should be made to ensure the study documentation is complete and will be stored securely for the required time period. Close out checks can be carried out by on-site or central monitoring.

10.2 Appendix 2. Guidance on the focus and intensity of monitoring

		Concerns identified in the assessment of risk associated with the design, methods or conduct of the trial (other than the intervention) which remain after mitigations are in place	
		No	**Yes**
Risk associated with the intervention /IMP	**Type A**	**Low intensity** Central monitoring of protocol adherence and data quality. No requirement for site visiting unless there are concerns identified from central monitoring that cannot be addressed by other means	**Low+** As outlined in A, plus appropriate monitoring to address the specific vulnerabilities associated with trial design, methods or conduct identified in the risk assessment.
	Type B	**Moderate intensity** Central monitoring 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 B, plus appropriate monitoring appropriate monitoring to address the specific vulnerabilities associated with trial design, methods or conduct identified in the risk assessment.
	Type C	**Higher intensity** More intense monitoring than above to have confidence in the completeness and reliability of safety data	**Higher+** As outlined in C, plus appropriate monitoring to address the specific vulnerabilities associated with trial design, methods or conduct identified in the risk assessment.

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CONFIRMATION OF SOP TRAINING RECORD

A copy of this record may be kept in your personal training file to confirm your training in a specific SOP. If required by a study Sponsor a record may also need to be kept in the Trial Master Files (TMF) or Investigator Site Files (ISF)

SOP Details: To be completed by the SOP Controller	
Title of SOP	Standard Operating Procedure (SOP) for Developing a Monitoring Plan for Studies Sponsored by PHT
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Personnel Details	
Name	
Job Title & Research Role	
Date of Training	
Nature of Training	Self Directed/Delivered by etc
Records of any meetings to clarify details in SOP	

Signatures
I confirm that I have read and consider myself to be sufficiently trained in the above Standard Operating Procedure with regards to my individual roles and responsibilities Signature of Trainee …… Date ……
I confirm training in the above SOP was delivered as recorded above and that the trainee may be considered sufficiently trained in their roles and responsibilities Signature of Trainer …… Date ……

Additional Notes & Signatures
Signature of Trainer (where appropriate) I confirm training in the above SOP was delivered as recorded above and that the trainee may be considered sufficiently trained in their roles and responsibilities Signature of Trainer …… Date ……..