Document Title: Monitoring Research Studies – Specific Considerations for the Risk Adapted Monitoring of CTIMPs or Device Studies

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Summary of Amendments

Version Number	Modification:
1.0	New SOP re-written for Royal Papworth Hospital sponsored CTIMP or device studies.

Key related documents:	Trust Research Policy Trust Policy DN1 Document Control Procedures SOP016: Monitoring Research Studies SOP071 Urgent Safety Measures FRM024 Risk Assessment Form for Papworth Sponsored CTIMPs FRM044: Pharmacy Monitoring Form

	FRM070: Pharmacy File Index TPL019: Monitoring Plan Template

Key Points of this Document

- This document sets out the roles, responsibilities and procedures to be followed by Royal Papworth Staff who are involved in the monitoring of Royal Papworth sponsored or managed Clinical Trials of Investigational Medicinal Products (CTIMPs) or device studies and sets out specific considerations for the monitoring of CTIMPs or device studies over and above the monitoring process set out in SOP016: Monitoring Research Studies.
- This SOP must be read in conjunction with SOP016: Monitoring Research Studies which details the monitoring process.
- It aims to provide clear guidance on the risk adaptations to monitoring according to the CTIMP or device categorisation; the monitoring process - including the procedure to be followed prior to, during and after a monitoring visit.
- The document is to be followed for Royal Papworth sponsored or managed CTIMP or device studies.

1 Purpose and Contents

a. This document defines the Trust's procedures for the monitoring of CTIMP or device studies either sponsored by Royal Papworth NHS Foundation or managed by PTUC.

b. The document describes the purpose of monitoring as described in Good Clinical Practice:

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

c. The document contains guidance on how monitoring visits should be scheduled, performed, and documented so as to comply with the Trust-wide policies on Information Governance and patient confidentiality.

2 Roles & Responsibilities

a. This Policy applies to all personnel that are conducting CTIMP or device studies only at the Trust.

b. Staff involved in the monitoring of studies must comply with the requirements set out in section 4.

c. The sponsor takes responsibility for the monitoring of the study but may delegate the task to an appropriately trained member of the study team (The Monitor).

d. Monitors should be independent of the work being reviewed.

e. Monitors should be appropriately trained, they should have the scientific and/or clinical knowledge needed to monitor the study adequately, including being competent in accessing and using Royal Papworth's electronic patient records. Evidence of training will include:

- Attended either external monitoring qualification and/or Attended Royal Papworth Internal monitoring course.
- Received training on Royal Papworth Electronic medical records system.
- Studies will be allocated based on previous monitoring experience.

f. The QA Manager will maintain a log of all staff who have received monitoring training (Monitors qualifications will be documented). The log will also document the types of studies previously monitored to define a level of experience. Only once it is deemed by the QA Manager that the specific individual has gained sufficient experience in monitoring of non-CTIMPS, will that individual be permitted to progress to monitoring CTIMPS or device studies.

g. Monitors should be thoroughly familiar with the protocol, written informed consent form and any other written information to be provided to subjects, along with SOP's, GCP, IB, SmPC, RSI and the applicable regulatory requirements.

h. The Principal Investigator (PI) and the research team must co-operate and assist the monitor throughout the complete process of monitoring.

i. Copies of all templates and guidance documents can be found on IQM and the Research and Development website:

https://royalpapworth.nhs.uk/research-and-development/information-researchers/standard-operating-procedures-2

3 Policy

a. This SOP is mandatory and, as per the Trust's Information Governance and Records Management framework, non-compliance with may result in disciplinary procedures.

4 Procedure

This SOP must be read in conjunction with SOP016: Monitoring Research Studies which details the process of monitoring.

4.1 Development of the monitoring plan

a. The sponsor is responsible for ensuring that a monitoring plan is approved prior to the start of a study. However, the development of the monitoring plan should be completed as an integral part of the protocol development and study set-up, and should include the CI and trial team, including the identified monitor for the trial wherever possible, in order to ensure that the monitoring processes ultimately documented within the monitoring plan are relevant, specific and achievable.TPL019 – Monitoring Plan template is available on the R&D website page.

b. The monitoring plan will be written taking into consideration the Risk Assessment form (FRM024) completed for the CTIMP or device study. The risk assessment form will allow considerations for any identified risks to be incorporated into the monitoring plan and will provide a guide for the type of monitoring, frequency and extent of the monitoring required. (Appendix 1 classifies the risk for CTIMPS and devices). Risks can be monitored a number of ways, often with a combination of the types of monitoring outlined below. This mixed method approach could provide a more comprehensive overview of the trial.

4.2 Considerations for types of monitoring

Central Monitoring:
ICH GCP E6(R2) addendum defines centralised monitoring as follows:

5.18.3: "Centralized monitoring is a remote evaluation of accumulating data, performed in a timely manner, supported by appropriately qualified and trained persons (e.g. data managers, biostatisticians)."

It is the process of using data stored centrally (e.g. at a CTU) to monitor processes at sites. Centralised monitoring can either be:

1. Programmed: i.e. programming that is integral to the trial database being used such as reference ranges for specific data values
2. Manual: by running predefined reports generated by the trial database which should be reviewed at regular predefined intervals.

Centralised monitoring can be used to observe the following:

- Missing data
- Inconsistent data
- Data outliers
- Unexpected lack of variability
- Protocol deviations
- Data trends such as range, consistency, and variability of data within and across sites
- Evaluate for systematic or significant errors in data collection and reporting or potential data manipulation
- Analyse site characteristics and performance metrics

4.3 Prior to initiation of the study

a. Prior to the initiation of the study, predefined quality tolerance limits should be agreed in order to identify systematic issues that may impact the safety of study subjects or the reliability of the study results. The setting of predefined tolerance limits is the responsibility of the study sponsor and should take into consideration the medical and statistical characteristics of the trial variables as well as the statistical design of the study.

For further information on this please refer to the following publication:

"Development of a standardised set of metrics for monitoring site performance in multicentre randomised trials: a Delphi study."
Whitham et al: Trials (2018) 19-557

b. Detection of deviations from the agreed tolerance limits must trigger an evaluation in order to determine what further action is needed which would usually be an on-site monitoring visit.

4.4 Types of monitoring to consider

a. On- site Monitoring:

On-site monitoring is the process of evaluating clinical trial procedures at the investigation site. Monitoring is carried out in person by the sponsor or their representatives, overseeing trial processes at sites where the research is taking place.
On-site monitoring is the most traditional form of clinical monitoring and is used commonly across site-based clinical trials. This is sometimes referred to as clinical site monitoring.
This type of clinical monitoring is most appropriate for trials that take place at a centralised investigation site. However, on-site monitoring is less practical for clinical trials that are spread across multiple investigation sites – especially if sites are not located nearby.

b. Remote Monitoring:

Remote monitoring oversees clinical trial research, evaluating the study off-site. Monitoring is carried out away from the investigational site where the research is taking place.
This type of clinical monitoring became much more common during the COVID-19 pandemic, when on-site visits were limited due to restrictions and safety measures. On-site monitoring became impossible, and so remote monitoring became the most effective solution.
Even now, after many COVID-19 restrictions have ended, remote monitoring remains an effective way to observe and track clinical trials. As a method that requires no face-to-face interaction with patients or site personnel, remote monitoring comes both with less risk to patients and a lower cost for the study.
Remote monitoring can also improve communication between the site and the sponsor. Most technology systems allow monitoring personnel and sponsors to share notifications, messages and other information – all in one streamlined platform.

c. Hybrid Monitoring:

Hybrid monitoring describes the method of completing monitoring by combining on site monitoring (face to face) with remote monitoring. By considering the risk assessment completed at the start of the study, an evaluation can be made about which elements of the monitoring need to be completed as a face-to-face visit and which can be completed remotely. This can vastly reduce the burden on the sponsor and the site alike.

d. Blinded studies:

The requirement for a separate blinded and un-blinded study monitoring in the case of blinded studies must be considered. If a study is blinded then it is best practise for the study to have two monitors: one who will monitor the blinded aspects of the study e.g. TMF/consent, and one who will monitor the un-blinded aspects of the study – (in the case of a CTIMP this would usually be all pharmacy related aspects of the study). This must be considered and agreed prior to the beginning of the study and delegated within the delegation log. Consideration must also be given as to where monitoring reports generated by the different monitors will be filed/stored so as not to cause accidental un-blinding of any study subjects.

4.5 Focussing on your plan

a. Monitoring activities should focus on preventing or mitigating important and likely sources of error in the conduct, collection, and reporting of critical data and processes necessary for patient protection and study integrity.

b. Based on the outcome of the risk identification, the monitoring should include the methods, responsibilities, and requirements for the trial to be monitored. Where applicable, the monitoring plan should address specific areas of the study that have been identified by the risk assessment.

c. The plan should be communicated to relevant parties (e.g. CI, monitors, project managers, data managers, statisticians etc.) and should provide those involved in monitoring with adequate information to effectively carry out their duties.

d. The Monitoring Plan should be reviewed annually and revised in a timely manner if any of the following occur during the lifetime of a study:

- protocol amendment
- increase in the number of protocol deviations
- Identification of new risks to study integrity, for example, new version of IB/SmPC
- Unexpected/unanticipated safety event, including Urgent Safety Measures (For more information please refer to SOP071)

e. For multi-centre studies, a separate monitoring plan for each site should be considered taking into account variations in local capacity and capability. If this is deemed necessary, then the same process for risk assessment review and mitigating actions must be undertaken for each site independently.

4.6 Pharmacy Monitoring

All Pharmacy monitoring must be carried out by completion of FRM044: Pharmacy Monitoring Form. This aligns specifically with the FRM070: Pharmacy File Index in order to facilitate completion of all sections relevant to pharmacy monitoring.

CTIMP pharmacy files will usually be stored within the pharmacy department and the trial master files must include a file note to document the location of the integral pharmacy files.

5 Risk Management / Liability / Monitoring & Audit

a. The R&D SOP Committee will ensure that this SOP and any future changes to this document are adequately disseminated.

b. The R&D Department will monitor adherence to this SOP via the routine audit and monitoring of individual CTIMP and device studies, and the Trust's auditors will monitor this SOP as part of their audit of Research Governance. From time to time, the SOP may also be inspected by external regulatory agencies (e.g. Care Quality Commission, Medicines and Healthcare Regulatory Agency).

c. In exceptional circumstances it might be necessary to deviate from this SOP for which written approval of the Senior R&D Manager should be gained before any action is taken. SOP deviations should be recorded including details of alternative procedures followed and filed in the Investigator and Sponsor Master File.

d. The Research and Development Directorate is responsible for the ratification of this procedure.

Further Document Information

Approved by: *Management/Clinical Directorate Group*	Research and Development Directorate
Approval date: *(this version)*	Current approved version date
Ratified by Board of Directors/ Committee of the Board of Directors:	STET
Date:	N/A
This document supports: *Standards and legislation*	Medicines for Human Use (Clinical Trials) Regulations 2004 and all associated amendments. UK Policy Framework for Health and Social Care Research (2023)

Equality Impact Assessment: Does this document impact on any of the following groups? If YES, state positive or negative, complete Equality Impact Assessment Form available in Disability Equality Scheme document DN192 and attach.

Groups	Disability	Race	Gender	Age	Sexual orientation	Religious & belief	Other
Yes/No	NO	NO	NO	NO	NO	NO	NO

Positive/Negative							
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Appendix 1

			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.