Document Title: Monitoring Research Studies – not requiring MHRA approval

Document Number: R&D SOP016

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Summary of Amendments

Version Number	Modification:
Version 7.0	SOP Re-written for Royal Papworth Sponsored Non CTIMP studies
Version 9.0	External Monitoring section removed
Version 10	Changes throughout the document

Related Documents	SOP083 Monitoring Research Studies – Specific Considerations for the Risk Adapted Monitoring of CTIMPs or Device Studies SOP025: Assessment and Registration of Trust Risk Rating for Research Studies SOP050 Handling of Protocol Non-Compliance SOP051 Serious Breach of Protocol or GCP in CTIMPs & Non-CE Marked Devices FRM027 Template Monitoring Log

	FRM038 Protocol Non-Compliance Form FRM054 Site Visit Log TPL010 Monitoring Visit Report Template TPL013 Confirmation of Monitoring Visit Template Letter TPL019 Monitoring Plan TPL024 Source Data Identification List TPL026 Investigator & Study Site Close-Out Visit Report Template TPL027 Study Close-Out Letter Template TPL033 Site File Report Template TPL034 Remote Monitoring Checklist Aid Memoir TPL035 Monitoring Follow Up Letter GD015 Monitoring & Audit Random Sample Selection GD021 OpenClinica User Guide for Monitors

Abbreviations:

AE	Adverse Event
CAPA	Corrective Action, Preventative Action
CI	Chief Investigator
CRF	Case Report Form
CRN	Clinical Research Nurse
CV	Curriculum Vitae
EMR	Electronic Medical Records
GCP	Good Clinical Practice
GP	General Practitioner
MHRA	Medicines & Healthcare Products Regulatory Agency
PI	Principle Investigator
PIS	Patient Information Sheet
QA	Quality Assurance
QC	Quality Control
R&D	Research & Development
RGPAS	Research Governance Project Approval System
SAE	Serious Adverse Event
SDV	Source Data Verification
SOP	Standard Operating Procedure
SUSAR	Suspected Unexpected Serious Adverse Reaction

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 studies – other than studies requiring MHRA approval. These are covered in SOP083.
- It provides guidance on the monitoring process; including the procedure to be followed prior to, during and after a monitoring visit.

1 Purpose and Contents

a. This document defines the Trust's procedures for the monitoring of Royal Papworth NHS Foundation Trust sponsored research studies (for additional requirements please see SOP083 Monitoring Research Studies – Specific Considerations for CTIMPs or Device Studies) or those hosted by Royal Papworth NHS Foundation Trust.

b. It documents the purpose of monitoring as described in Good Clinical Practice (GCP: 'a standard for the design, conduct, performance, monitoring, auditing, recording, analyses, and reporting of a clinical trials that provides assurance that the data and reported results are credible and accurate, and that the rights, integrity, and confidentiality of the trial participants are protected').

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 research 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, 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

f. Studies will be allocated based on previous monitoring experience

g. 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.

h. Monitors should be thoroughly familiar with the protocol, written informed consent form and any other written information to be provided to participants, SOP's, GCP, and the applicable regulatory requirements.

i. The PI and the research team must co-operate and assist the monitor throughout the process of monitoring.

j. Copies of all templates and guidance documents can be found on 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

4.1 Monitoring plan process

a. Prior to the start of the study the Sponsor will determine the appropriate extent and nature of monitoring arrangements based on the objective, purpose, design and complexity of the trial. This will be agreed at Research Governance Project Approval System (RGPAS) meeting as part of the local approvals process. (See SOP025: Assessment and Registration of Trust Risk Rating for Research Studies). A monitoring plan (TPL019) will be created either by the QA Manager or QA Monitor before the study starts. Taking into consideration the risk assessment, the plan will detail the type of monitoring (on-site, remote or hybrid), the expected frequency of monitoring visits, amount of source data verification required and if the site/sponsor files need to be reviewed. The study will be added to the department's monitoring rota and a monitor assigned.

- 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.

- 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.

- 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.

b. If Royal Papworth NHS Foundation Trust is the sponsor of a multi-centre study the extent or nature of monitoring additional sites will be determined during study set-up. Each site may have their own site-specific risk adapted monitoring plan (see section 4.1.c.)

c. Monitoring plans shall be risk adapted to ensure they remain fit for purpose. If any of the events listed below occur an additional risk assessment shall be undertaken.

1. Concerns are raised regarding research practice
2. Monitoring of other research studies has highlighted concerns
3. Substantial amendments and subsequent risk assessment indicate a change in risk
4. Audit or monitoring finds serious non-conformities
5. A change in the PI or CI
6. A serious breach
7. SAE
8. SUSAR
9. Site specific issues:

This rolling review will be maintained by the monitor/research team/QA team to amend/adapt the monitoring plan as appropriate dependant on findings or triggered visits.

Risk/Issue Area	Examples Of Events/Incidences
Site performance	Site/s recruiting very higher number of patients (higher PRR than expected) Site/s with significantly high screening failure rate Site/s with high patient discontinuation rate
Data quality	Site/s showing continuous outlier, inconsistencies or abnormal distribution of critical efficacy & safety data Site/s missing critical data points (missing data)
Patient safety	Site/s showing higher or lower per patient AE/SAE rate than other sites Site/s missing SAE reporting in time Site/s with significant number of patients discontinued due to AE/SAEs
Study conduct /protocol specific study procedure deviation/violation	Site/s not performing protocol specific procedure on time (e.g. for a study , MRI to be taken exactly 1 hr after study drug intake)
Important protocol deviation or violation	Site/s recruiting patient not fulfilling key eligibility criteria Site/s showing patients' visits happening consistently out of window period
Patient compliance	Site/s with patients with missing study drug administration Site/s with patients missing subject diary

4.2 Preparation for the monitoring visit

a. The monitor will schedule the monitoring visit, contacting the PI, study team and other relevant departments in advance. If required a monitoring visit can be split over a number of days.

b. If applicable the monitor will identify any paper or electronic documents that are required and inform the study team.

c. Advanced selection of participants will be performed so as to allow the appropriate paperwork (CRF's, paper medical notes or EMR etc.) to be supplied. (Please see a member of data management if the participants are to be randomly selected, the process can be found in guidance document GD015 Monitoring & Audit – random sample selection). An email confirming arrangements for the visit based on the format found in TPL013 (Confirmation of monitoring visit letter) will be sent. This will contain details of what will be monitored: e.g. site file, electronically stored data, the study ID of participants to be monitored.

d. The monitor will request the study team provide a table with the location of every piece of source data (TPL024 Source Identification List).

e. If the study is using OpenClinica the monitor should arrange access and any other additional training with a member of Data Management. (Please also reference GD021 OpenClinica User Guide for Monitors).

f. The monitoring report from previous visits will be reviewed to identify any outstanding actions that need to be re-visited.

g. If the monitoring visit is triggered due to a specific problem, the monitor will inform the research nurse/co-ordinator of any specific requirements before-hand.

4.3 During the monitoring visit

a. The monitor will complete a report log (FRM027 Case Report Form Log) for each study participant to keep a record of the source data and case report forms reviewed at each monitoring visit.

b. The monitor will complete Source Data Verification (SDV). SDV is the act of verification of the data presented in case report forms with the source data, conducted to ensure that the data collected are reliable and allow for reconstruction and evaluation of the trial.

c. The e-site file and e-Sponsor file will be checked using the reporting templates (TPL033 and TPL010) to ensure that all the required regulatory documentation has been filed and the

current approved versions are present. If applicable a summary of action points will be documented to follow up.

d. Specific study logs should be checked. For example, screening and enrolment logs/ SAE/Protocol non-compliance logs.

e. If any SAE's have occurred the monitor will check they have been reported appropriately to the sponsor and the necessary regulatory bodies, and that the required timelines for review and assessment have been adhered to.

f. Where protocol deviations have occurred, they will be reviewed to ensure adherence to SOP050 Handling of Protocol Non-Compliance. FRM038 Protocol Non-Compliance Form will be used to document the non-compliance; measures to prevent any re-occurrence should also be documented.

g. A non-compliance that has (or has the potential to) affect the safety, physical or mental integrity of the participant or has (or has the potential to) affect the scientific validity of a clinical trial shall be treated as a serious breach (SOP051). These findings will be highlighted to the research team during the monitoring visits, following further discussion and investigation, may be confirmed or downgraded to a non-compliance.

h. Particular attention will be made to checking the informed consent process:

1. The informed consent will be cross referenced with the GP letter (if applicable), CRF and medical records to check the participant's identity and that the date of the informed consent was before any trial related procedure occurred.

2. It will be verified that the consent process allowed adequate time for the participant to discuss the trial with their family / GP etc.

3. The informed consent form will be checked to make sure all applicable sections have been completed by the participant; that the boxes contain the participant initials and the participant has printed their own name, date and signed the consent form.

4. The signature of the person taking consent will be checked against the delegation log.

5. The version of the consent form will be checked to make sure it was signed after all appropriate approvals were in place.

6. If applicable, participants have received revised information and signed the revised consent form.

7. It will be checked that the original consent form is in the site file, a copy is uploaded to the patient's electronic medical records, and a copy is given to the participant. If

this sequence of documentation has not been followed a file note will be placed in the site file.

8. The monitor will check that the consent process has been fully documented in the patient's electronic medical records, the R&D "P Form" has been completed with the details of the study and the PIS has been uploaded to EMR. The same process should be followed for any other electronic medical record platform at other sites.

i. Where OpenClinica is used for data capture the monitor will be responsible for checking the audit trails – 100% of audit trails will be reviewed for all patients monitored:

1. Checks will include that the PI Assessment and Medical Assessment have been completed and signed by the PI.

2. The severity and relatedness of AE/SAEs are all completed by the PI or sub-investigator (The delegation log should be checked for those signed off to complete AE/SAE reporting).

3. The Sponsor SAE assessment has been completed and signed by the R&D Director.

j. The monitor is responsible for checking that any errors identified in previous monitoring visits have been rectified and that any queries have been signed off.

k. Other applicable supporting departments will also be monitored periodically as detailed in the monitoring plan.

l. At the end of the visit the monitor should liaise via email with the CRN/trial co-ordinator and PI to discuss any findings and resolve any queries found during the review of the data (face to face meeting to be held if required). Any closed queries will still be included in the monitoring report, but these will be for information only.

m. Any follow up correspondence should indicate the number of findings identified with an agreement regarding the deadline for responses to all findings; however, all findings must be resolved within a maximum of four weeks. The monitors site visit log FRM054 must be completed for the monitoring visit, and the member of the research team available for the monitoring visit must counter sign the form.

n. Additional monitoring may be undertaken in response to concerns raised re: data quality, patient safety and recruitment or other concerns.

4.4 Monitoring report

a. The monitor must complete the e-site file and e-Sponsor file reporting templates (TPL033 and TPL010) and the Case Report Form log (FRM027) within 5 working days of the monitoring visit, unless further clarification or information is required.

b. The monitoring report will detail the records that have been reviewed, any queries / discrepancies raised and any changes that need to be made. If required a summary of action points should be compiled using the table within the Site File Report template.

c. If there are no findings raised this should be indicated in the summary table or follow up letter.

d. Re-occurring discrepancy notes (DNs) should be brought to the attention of the Data Management Lead. In some instances, multiple DNs may result in a design change which may undo CRFs which have previously been SDV'd. If this happens, the audit trail should be checked and the data re-SDV'd.

e. A follow up email will be completed (TPL035 Monitoring Visit Follow up Template Letter) which will include feedback on the quality of the data and the progress of the study at the site. The letter and the monitoring reports should have timelines for the resolution of queries (recommend 4 weeks); as well an anticipated date for the next monitoring visit.

f. The monitoring reports and follow up letter will be sent (via email) to the CRN/ Co-ordinator /PI for any queries / discrepancies to be amended within the specified timelines. The study team should aim to have queries resolved and the reports signed within the recommended 4 weeks**.** Any queries that cannot be completed within the specified timelines will be followed by the study team after the monitoring visit. The monitor will follow these and all other queries up at the next monitoring visit to confirm completion.

g. If the study team does not resolve the monitoring queries, the study will be escalated to the QA meeting where the study team will be expected to provide reason for not completing within the agreed timelines.

h. In the event of the study being multi-centred the monitoring report should be sent to the study manager for QC checks prior being sent out to the sites. Trial manager will then forward the report to the site.

i. Once the data queries / actions have been resolved a copy of the final report will be sent to the PI for signature.

j. The signed monitoring report will be scanned and uploaded to the monitoring section of the e-site file.

k. If any concerns are raised by the monitor these should be addressed by the study team. If the monitor feels their concerns are not being resolved then they will inform the project

manager who, when appropriate, will escalate the issues to the R&D QA meetings for appropriate actions. Consistent issues with monitoring or audit that cannot be resolved at this level will be further escalated to the Research and Development Directorate (RDD) by way of the quarterly report submitted to this meeting.

l. The CAPA database will be used by QA to document deviations, breaches or other concerns escalated to the team which may require further investigation or intervention. The CAPA database will record these findings, with CAPA process form in IQM used to investigate root cause analysis.

m. All monitoring reports for Royal Papworth Sponsored and Non-sponsored studies must be submitted to R&D QA at randdqa@nhs.net.

5 Central Oversight – Remote 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:

Programmed: i.e. programming that is integral to the trial database being used such as reference ranges for specific data values;

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
- Discrepancy notes
- 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

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

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

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.

Remote monitoring checklist/Aid memoir is available to reference (TPL034)

6 Triggered Monitoring

a. Centralised/remote monitoring or general concerns expressed by a member of the project team may result in an off-plan monitoring session. This may require a more in-depth assessment of a site, or a review of the risk categorization and revision of the monitoring plan (TPL019). In this case a monitoring visit will be arranged to assess the issues and future monitoring requirements.

7 Close out visit

a. The monitor should complete a close out visit for the study by completing TPL026 (Investigator and study site close out visit report) in conjunction with the study team. The report will be used to guide the monitor when completing a final review of the paper, e-site and sponsor files in preparation for archiving.

b. The close out visit report may need to be completed over several visits. There is a separate form on the report to document follow up actions that need to be completed prior to archiving. Once all actions are completed and documented, the close out visit report should be signed, dated and filed in the monitoring section of the site file.

c. TPL027 Study close out letter should be sent to the Investigator of the study. The letter formally closes your monitoring of the study and reminds the investigator of any continuing trial obligations (e.g. archiving). A copy of the letter should be filed along with the study close out report in the site file.

8 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 clinical trials 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.

Approved by: *Management/Clinical Directorate Group*	Research and Development Directorate
Approval date: *(this version)*	Current active version approved 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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