Royal Papworth Hospital
NHS Foundation Trust

Document Title: Monitoring Research Studies – Royal Papworth Sponsored non CTIMPs

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Staff involved in development: *Job titles only*	Senior R&D Manager, R&D Operational Manager, Clinical Project Managers
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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**

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 Non-CTIMP research studies.

- It provides guidance on 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 Non-CTIMPS and Non Royal Papworth sponsored studies.

1 Purpose and Contents

a. This document defines the Trust's procedures for the monitoring of Royal Papworth NHS Foundation Trust sponsored research studies and research studies (non-CTIMP – for additional requirements for CTIMPs please see SOP083) or 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 subjects 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 appropriately trained, have the scientific and/or clinical knowledge and be competent in accessing and using Royal Papworth's electronic patient records. Evidence of training will include:

   i. An external monitoring qualification and/or attendance at the Royal Papworth Internal monitoring course.

ii. Royal Papworth mandatory e-Health Lorenzo EPR training & Lorenzo request and results training.

Studies will be allocated based on previous monitoring experience.

e. Monitors should be independent of the work being reviewed. The Monitoring & Audit Co-ordinator will maintain a log of all staff who have received monitoring training which will also further define the studies they have monitored in order to define experience. Only once it is deemed by the senior management/QA Team that the specific individual has gained sufficient experience in monitoring of non-CTIMPS, will that individual be permitted to progress to monitoring CTIMPS.

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

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

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

https://royalpapworth.nhs.uk/research-and-development/informationresearchers/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 The Purpose of Monitoring

a. The purpose of monitoring a study is defined in GCP as ensuring that:

1. The rights and well-being of study human subjects 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/amendments(s), with GCP, and with the applicable regulatory requirement(s).

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) as part of the local approvals process. (See SOP025: Assessment and Registration of Trust Risk Rating for Research Studies). Based on the risk rating; a monitoring plan (TPL019) will be created by the Monitoring & Audit Co-ordinator before the study starts, detailing the expected frequency of monitoring visits and the amount of source data verification required as per the RGPAS meeting. The study will be added to the departments monitoring rota and a monitor assigned.

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 will have their own site specific risk assessment and 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 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, medical notes 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 GL015 Monitoring & Audit – random sample selection). An email confirming arrangements for the visit based on the format found in TPL013 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 within the electronic medical notes (TPL024).

e. If the study is using OpenClinica the monitor should arrange access and any other additional training with a member of Data Management.

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) 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 logs as defined in the study protocol should be checked. For example, screening and enrolment 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 Lorenzo/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 esite file.

8. The monitor will check that the consent process has been fully documented in Lorenzo, 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, relatedness & expectedness 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 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. If any of the discrepancies require the study database to be changed than a Data Amendment form FRM002 needs to be completed. If the discrepancy is a CRF design change then FRM037 is to be completed, these are to be sent to the data manager.

e. In the event of design changes un-doing the data which is SDV'd:

1. The design must be approved knowing the SDV will be undone.

2. Data manager creates a list of SDV'd patients or CRF's that will be affected by the change on FRM039.

3. The change is implemented.

4. The monitor uses the list provided to review the audit log for each patient's CRF to review any changes made to the CRF since previous SDV. If there are no changes then

the SDV can simply be remarked. However, if there are changes then the monitor would have to repeat the process of data SDV.

f. 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.

g. The monitoring reports and follow up letter will be sent (via email) to the CRN/ Coordinator /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.

h. 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.

i. 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.

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

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

l. 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 quarterly to this meeting.

m. 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 used to investigate root cause analysis.

n. 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

b. 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, esite and sponsor files in preparation for archiving.

c. 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.

d. TPL027 Study close out letter should be sent to the Investigator of the study. The letter formally closes your monitoring of the study, 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.

Further Document Information

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 (2018)
Key related documents:	Trust Research Policy [Insert list of linked or relevant documents to this SOP]

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							

Review date:	January 2025

I certify the contents of this SOP has been reviewed and ratified

Dr Patrick Calvert 12-Mar-2022

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Signed by Dr Patrick Calvert, Clinical Director of R&D Date