STANDARD OPERATING PROCEDURE

S19 – Monitoring

Version	6
Effective Date	16th November 2021
Review Date	15th November 2024
Author & Position	Ali Kerridge, Assistant Research & Development Manager
Signature	
Date	8 DEC 2021
Approver & Position	Helen Quinn, Research & Development Director
Signature	
Date	25 NOV 2021

Controlled document

This document has been created following the Royal Devon and Exeter NHS Foundation Trust Policy for the Development, Ratification & Management of Procedural Documents. It should not be altered in any way without the express permission of the author or their representative.

It is the responsibility of all users of this SOP to ensure that the correct version is being used. If you are reading this in a paper format please go on-line to confirm you have the latest version.

DISCLAIMER

This generic R&D Standard Operating Procedure (SOP) must be followed unless a study specific SOP exists.

Once printed this is an uncontrolled document

Full History			
Version	**Date**	**Author**	**Reason**
1.0	27 April 2011	PenCLRN Assistant Research Manager	New SOP to reflect process
2.0	12 September 2013	Assistant R&D Manager	Inclusion of comments following audit of SOP. Change to SOP title to reflect inclusion of all sponsored research. Change to SOP to include monitoring of all RDEFT sponsored studies. Appendix 1 updated.
3.0	22 September 2014	Acting Assistant R&D Manager	Outlining responsibility for escalation of unactioned/ unresolved monitor findings. Update to monitor plan template (appendix 4)
4.0	30 January 2015	Assistant R&D Manager & R&D Coordinator	Amalgamation of SOP and WI. Clarification of levels of monitoring and timeframes for reporting findings/responses being received. Amendment to monitoring plan example.
5.0	06 April 2018	Assistant R&D Manager	Updating to new SOP template. Update to reference new UK policy framework. Addition of other methods of monitoring eg introduction of oversight meetings, central monitoring
6	16 November 2021	Assistant R&D Manager	SOP update and incorporation of Remote Monitoring.

Associated Trust Policies/ Procedural documents:	Monitor plan Risk Assessment
Key Words:	R&D Monitor Clinical Trial SOP

In consultation with:

- Research & Development – Quality Assurance Group (QA)
- Research & Development Governance and Oversight Group (GOG)

Contents

1 INTRODUCTION 4

2. PURPOSE 4

3. SCOPE 4

4. DEFINITIONS 4

5. DUTIES AND RESPONSIBILITIES OF STAFF 5

6 PROCEDURES 5

6.1 MONITORING PLAN AND EVALUATION OF MONITORING LEVEL 6

6.1.1 Level 1 Quality Control 6

6.1.2 Level 2 Monitoring 6

6.1.3 Level 3 Monitoring (primarily for CTIMPs, Medical Device Trials and High Risk Interventions) 7

6.2 MONITORING VISIT ACTIVITIES 8

6.2.1 Before a Monitoring Visit 8

6.2.2 At a Monitoring Visit 8

6.2.3 After a Monitoring Visit 10

7. DISSEMINATION AND TRAINING 10

8. MONITORING COMPLIANCE AND EFFECTIVENESS OF THIS SOP 10

9. ARCHIVING ARRANGEMENTS 11

10. REFERENCES 11

1 INTRODUCTION

The conduct of Research is a co-operative undertaking between the Sponsor and Chief Investigator (CI). Each is responsible for ensuring that the conduct of the research conforms to the Protocol and adheres to the applicable laws and regulations as driven by the Department of Health's UK Policy Framework for Health and Social Care Research and the Medicines for Human Use (Clinical Trials) Regulations. The Royal Devon & Exeter NHS Foundation Trust (hereafter termed as 'the Trust') has a responsibility for oversight of research conducted on its premises or which it sponsors. Consequently, the Research & Development Department (R&D) undertakes to monitor research conducted when the Trust is acting as a research sponsor. The responsibility involves regular and conscientious review of the progress of the study by a range of 'monitoring activities' performed on the CI site (and if applicable participating sites), at intervals appropriate to the size and risks of the research, and proper reporting of monitoring visits.

The purpose of monitoring is to ensure:

- That the dignity, rights, safety and wellbeing of the subjects participating in the study are protected.
- The conduct of the study is in compliance with the current approved Protocol/Protocol Amendment(s), with Good Clinical Practice (GCP) and with the applicable regulatory requirements.
- The reported trial data are accurate, complete and verifiable from the source.

2. PURPOSE

This SOP describes the risk-based procedures that will be used by Trust R&D to monitor and give oversight of research sponsored by the Trust, conducted on Trust premises or which fall under a Service Level Agreement with other organisations.

3. SCOPE

This SOP is applicable to all research (both Clinical Trial of an Investigational Medicinal Product (CTIMP) and non-CTIMPs) sponsored by the Trust or, when the commitment to monitor has been delegated to the Trust by a non-commercial sponsor.

Where the Trust sponsors multi-centre research or CTIMPs, the responsibility to monitor may be delegated on a risk-based approach. Any delegation of monitoring responsibilities will be documented in writing. This SOP covers monitoring throughout the life of the research.

4. DEFINITIONS

AE	Adverse Event
CAPA	Corrective Action Preventative Action Plan
CI	Chief Investigator
CRF	Case Report Form
CTIMP	Clinical Trial of an Investigational Medicinal Product
CTU	Clinical Trials Unit
CV	Curriculum Vitae
DMC	Data Monitoring Committee
FPFV	First Patient First Visit
GCP	Good Clinical Practice
GOG	Research & Development Governance Oversight Group
HRA	Health Research Authority
ICH	International Conference on Harmonization
IMP	Investigational Medicinal Product
ISF	Investigator Site File

PI	Principal Investigator
QA	Quality Assurance
REC	Research Ethics Committee
RSI	Reference Safety Information
SDV	Source Data Verification
SAE	Serious Adverse Event
SIV	Site Initiation Visit
SOP	Standard Operating Procedure
Sponsor	An individual, company, institution or organisation which takes responsibility for the initiation, management and financing of a clinical trial. Sponsorship activities may be delegated to the Investigator, CTU and/ or other organisations as appropriate
SUSAR	Suspected Unexpected Serious Adverse Reaction
TMG	Trial Management Group
TSC	Trial Steering Committee

5. DUTIES AND RESPONSIBILITIES OF STAFF

The **Chief Investigator** (CI) or his delegated Trial Team Members has responsibility for conducting the Research according to the approved Protocol, complying with procedures necessary to secure the quality of every aspect of the trial, ensuring that all documentation is in an appropriate and secure location and enabling monitoring activities to be undertaken at the study site. They must ensure that all findings and any Corrective Action Preventative Action (CAPA) plans are addressed

The R&D Professional Services Team will, as part of the Sponsorship process for Research, conduct a risk assessment, the outcome of which will determine the type (eg on-site, central monitoring, management groups, recruitment etc) and amount (eg number of visits, what is being checked) of oversight required for a particular study. The risk assessment will be revisited, if necessary, prior to approval and/or during the study. A scheduled monitoring plan may then be developed to reflect this. Monitoring will be delegated to appropriately trained members of the R&D Office or, if applicable, to other suitable external parties eg a Clinical Trials Unit (CTU) or independent monitor. Monitors may not make visits until they have had adequate training and experience.

The Study Monitor is responsible for conducting the monitoring visit in accordance with the Monitoring Plan, this SOP (unless otherwise agreed and delegated) and regulatory requirements.

The **Sponsor** retains overall responsibility and should have oversight of the monitoring process. This includes reviewing monitoring reports/monitoring letters and advising of appropriate CAPA to be taken where necessary. The Sponsor will be responsible for the delegation of monitoring to other parties when applicable. This will be documented in writing.

6 PROCEDURES

Monitoring services are provided by R&D for Trust-sponsored studies unless delegated by the Sponsor. For other types of clinical studies, monitoring services may be provided when considered necessary.

Routine scheduling for monitoring of a study may be superseded by trigger monitoring in the following circumstances and priority:

- Report of a Serious Adverse Event (SAE) / Suspected Unexpected Serious Adverse Reaction (SUSAR) that has occurred on a Clinical Trial from any member of the Clinical Trial team.
- Report or suspicion of fraud and/or misconduct.
- Recruitment on a patient-patient basis on high-risk Trials which also use unlicensed medicines (i.e. Gene Therapy, Cellular Immunotherapy).
- Studies which have had a number of critical/major findings on a previous

monitoring visit.

6.1 MONITORING PLAN AND EVALUATION OF MONITORING LEVEL

The level of monitoring of investigator-initiated studies shall be defined by the Sponsor on a risk basis, prior to study initiation and documented in the study-specific Risk Assessment.

The risk assessments of all Trust sponsored studies will inform a monitor schedule that outlines which studies require level 2 and 3 monitoring (see section 6.1.2 & 6.1.3). This will be presented to the Governance Oversight Group (GOG) to demonstrate the Trust's oversight of sponsored studies.

In addition, for Trust sponsored CTIMP's, a study–specific monitoring plan will be drawn up. The study-specific monitoring plan defines instruction for the persons performing the monitoring at the site and must be agreed and signed off by the Sponsor. Changes or additions to the monitoring plan may be made during the course of the trial by mutual agreement with the Sponsor.

The level of monitoring should be based on an overall evaluation of the:

- Safety profile of the investigational medicinal product (IMP) and thereby the safety of the study participants
- Extent of intervention
- Recruitment rate
- Complexity of study design and organisation
- Study site and study personnel
- Resources

The organisation has defined three different levels of monitoring:
Level 1 quality control
Level 2 monitoring
Level 3 monitoring (primarily for CTIMPs.Medical Device Trials and High Risk Interventions)

6.1.1 Level 1 Quality Control

In order to comply with very basic quality control requirements every study sponsored by the Trust should include monitoring activities on Level 1, i.e. verification of:

- Study status
- Recruitment rates
- Time taken to First Patient First Visit (FPFV)
- Recruitment to Time and Target

The Level 1 quality control activities shall be documented electronically as part of the recruitment submission. Obvious shortcomings shall be communicated to the Governance Oversight Group (GOG) and corrective activities agreed upon with the CI/Sponsor.

6.1.2 Level 2 Monitoring

Level 2 monitoring activities include confirmation of the:

- Existence of signed Informed Consent Forms and verification of the existence of the subjects
- Existence and maintenance of a Trial Master File/Investigator Site File
- The use of Case Report Forms (CRF)
- An overall evaluation of actual study conduct as presented to and approved by a Research Ethics Committee.

The Level 2 monitoring activities shall be documented in the Monitoring Visit Report and the percentage of documents to be reviewed will be identified. Findings shall be communicated to the Investigator and corrective activities agreed upon. Typically, this compromises a single visit early in the life of the trial (see section 6.2 for more details).

6.1.3 Level 3 Monitoring (primarily for CTIMPs,Medical Device Trials and High Risk Interventions)

A monitoring plan will be created, based on the trial design (to inform the methods used), and a risk assessment (to determine the intensity and focus of the monitoring) carried out for each trial. Various approaches may be used e.g. trial oversight committees, central monitoring, on-site monitoring and site self-monitoring checks. The trial monitoring plan should be generated and reviewed by staff with an appropriate level of knowledge about the trial e.g. CI, Trial Coordinator, Research Governance & Quality (RG&Q) Manager or Assistant R&D Manager. The document should then be approved by the R&D Director. The following approaches may be considered:

6.1.3.1 Site Monitoring

On-site monitoring may be required, whereby the monitor will visit participating sites to review study conduct, adherence to the Protocol and International Conference on Harmonisation Good Clinical Practice (ICH GCP), participant eligibility and data collection. The role of the monitor is considerably greater than undertaking Source Data Verification and checking the Trial Master/Investigator Site file. These activities may not necessarily reveal issues at site; therefore, it is important that the monitor communicates effectively with the site personnel, including the Chief Investigator/Principal Investigator. Discussing the study with personnel may reveal variances that would otherwise not be identified through other methods.

At each site visit, the monitor should continually review the acceptability of site personnel, facilities and study progress. Any concerns must be raised with the site and escalated to the Senior Trial Manager for the study. Concerns regarding study conduct or potentially serious breaches or fraudulent activity must be raised with the RG&Q Manager. See section 6.2 for more details.

6.1.3.2 Trial Oversight Committees

Oversight is strongly recommended for all studies and this may be performed by a Trial Management Group (TMG), Trial Steering Committee (TSC), Data Monitoring Committee (DMC), and Sponsor Oversight Committee.

6.1.3.3 Central Monitoring

Central monitoring procedures should be employed where possible. These may include: remote review of study data for omissions, inconsistencies or invalid information; central review of consent forms, delegation logs and eligibility checklists; remote site training (eg through teleconferences); review of recruitment rates, rates of reporting, withdrawals and losses or rates of adverse events. Central statistical monitoring techniques may be used to compare data from different sites to identify sites that may warrant further investigation, site monitoring and/or support and training. Those central monitoring procedures relating to database management or statistical techniques should be documented in the Data Management Plan or Statistical Analysis Plan respectively.

6.1.3.4. Site Self-Monitoring

This may be utilised alongside central monitoring, where deemed appropriate, following completion of the study risk assessment. Sites complete a self-monitoring form which covers areas such as recruitment status, study participant documentation, status of approvals, content of the ISF and review of SAE forms. This may be carried out as a standalone exercise, or with support from the Trial Manager e.g. through a teleconference. The completed form is then returned to the Trial Manager for review and further action if required e.g. site monitoring visit or issuing of training.

6.1.3.5. Source Data Verification (SDV)

Monitoring should ensure that reported study data is complete, accurate and verifiable from source documents. This does not imply that every item of data recorded must be supported by a source document or checked, but where there are original documents, the study data should be in agreement with the information they contain. Statistically

controlled sampling may also be an acceptable method for selecting data to be verified. Site or even central monitoring may involve SDV on a minimum percentage of study data, or directed to more critical data for a particular study, such as consent, eligibility or endpoint data and/or SAEs. The monitoring plan should document what source documentation will be available for a particular study and the requirements for SDV.

6.1.3.6 Site Feasibility/Site Selection

All proposed research sites should undergo assessment prior to being confirmed as a study site. This is usually through the completion of a feasibility questionnaire. The site assessment should feed into the risk assessment as inexperienced investigators or those with a lower number of support personnel may require a higher intensity of monitoring.

6.1.3.7 Site Initiation

Site Initiation Visits (SIV) may be conducted at site. Site initiation should be completed prior to the recruitment of patients at site and once all of the approvals and site interventions are in place i.e. completed Green Light Procedure. All site initiation documentation, e.g. Attendance logs, SIV report, must be filed in the TMF/ISF.

6.1.3.8 Safety Monitoring

The review of Adverse Events (AEs) and SAEs is an integral part of monitoring patient safety. The monitor should verify that all AEs/SAEs have been identified, recorded and reported as required by the Protocol. In addition, each individual SAE must be checked for:

- Seriousness
- Causal relationship to intervention under study
- Expectedness – in CTIMPs this must be against the approved Reference Safety Information (RSI) for the IMP.

6.1.4 Remote Monitoring

In the event a Monitor is not able or permitted to access the premises for on-site Monitoring the RDE can support Telephone Monitoring, Self-Declaration Monitoring, RDE Monitoring and MS Teams with Screen Sharing Monitoring. Enquiries for further information can be made to the QA Manager at rde-tr.Research@nhs.net.

6.2 MONITORING VISIT ACTIVITIES

The monitoring visit activities should be defined in accordance with the study Protocol and, for Level 3 Monitoring, documented in the Monitoring Plan. The monitoring visits shall be documented in the Monitoring Visit Report(s).

6.2.1 Before a Monitoring Visit

Before each monitoring visit the availability of the study site personnel and access to required information should be ensured. The study monitor will become thoroughly familiar with the research prior to the monitoring visit, by reviewing the Protocol, particularly the Trial design, schedule of events, inclusion/exclusion criteria, treatment regimen, IMP supply, and SAE reporting. The Monitor may also review the ethics application and any written information to be provided to trial participants to gain further knowledge of the study.

6.2.2 At a Monitoring Visit

The first monitoring visit should be performed early in the study to capture and minimise any issues re-occurring. Follow-up visit(s) may be conducted during the recruitment period, as agreed with the CI/Study Team or after the recruitment has been completed, depending on the duration of the study and the number of participants to be recruited in the study. The last monitoring visit should be conducted after the last participant has completed his/her participation in the study and it may be considered a study completion visit. All monitoring visits should be scheduled upon the availability of the study personnel, and as agreed in the study approvals can be on-site or remote

On commencing a Site Monitoring, the Study Monitor should sign a Monitoring Visit Log. For visits lasting more than one day; the Monitoring Visit Log shall be signed for each day. A member of the study staff should countersign the log during the visit. The following should be considered as part of the monitoring exercise:

6.2.2.1 Study Progress

The progress of subject recruitment and participation and the recruitment rate (number of participants screened, enrolled, randomised, on-going, completed, discontinued and withdrawn) and whether the CRF entries and source documentation are up-to-date in relation to participant status should be discussed with the study staff.

6.2.2.2 Investigator Site File/Trial Master File

It should be ensured that all the required essential documents are available and properly maintained at the site. All the required reports, notifications, applications, submissions etc should be provided by the Investigator. These documents should be accurate, complete, timely, legible and dated, and identify the study. Should any of the essential documents be found missing or inadequate, this should be documented in the Monitoring Visit Report.

6.2.2.3 Investigator Qualifications, Resources and Facilities

In the case of any changes in study personnel, signed Curriculum Vitae (CVs) should be obtained from the new staff and their signatures added to the Delegation Log, which will be reviewed during the monitoring visit. For those study personnel undertaking consent on CTIMPs or non-CTIMP interventional studies, a copy of their latest GCP certificate must also be present.

6.2.2.4 Compliance with Protocol ICH GCP and Regulatory Requirements

It should be checked that the study personnel are performing study-specific functions in accordance with the approved Protocol (and its amendments when applicable) and have not delegated these functions to unauthorised persons. It must be verified that the Investigator is enrolling only eligible participants and that the study procedures have been conducted according to ICH GCP and applicable regulatory requirements.

6.2.2.5 Informed Consent

It should be verified that the correct approved versions of the Patient Information Sheet (PIS) and
Informed Consent Forms were used and that each participant's written informed consent was obtained before any study related procedures were performed. It should be checked that the participants or their legal representatives have signed and personally dated the Informed Consent Form. The Investigator/staff member who conducted the informed consent process should have countersigned and dated the Informed Consent Form and given a copy of the form to the study participant. This will be documented in the patients notes and on MyCare.

6.2.2.6 Case Report Forms and Source Documentation

It must be verified that source documents are accurate, complete, up-to-date and available. The accuracy, legibility, consistency and completeness of CRFs must be checked against the source documents in the extent defined in the Monitoring Plan. It should be ensured that all appropriate corrections or additions are made, dated and initialled by the Investigator or by another member of the staff authorised by the Investigator to make CRF changes. It must be ensured that all adverse events, serious adverse events and concomitant medications are appropriately recorded.

6.2.2.7 (Serious) Adverse Events / Serious Breaches

It must be verified that (serious) adverse events and (where identified) serious breaches have been reported and followed up appropriately and reported to the authorities (when applicable), as specified in the Protocol and in national regulations.

6.2.2.8 Investigational Medicinal Product

It must be checked that IMP accountability is adequately controlled and documented throughout the product flow at the study site (arrival, dispensing, use, return from the participant and destruction after the study). Storage times, conditions and expiry dates must also be acceptable and sufficient supplies available. In a double-blinded study, it should be verified that study staff have access to the treatment codes in case of an emergency and that any premature unblinding has been appropriately documented and explained.

6.2.2.9 Biological Samples

The labelling and storage of biological samples must be verified when applicable. It must be ensured that laboratory normal ranges and accreditations are up-to-date.

6.2.3 After a Monitoring Visit

The Study Monitor or another person who conducted the monitoring visit will report all significant findings, deviations, deficiencies, activities, discussions and conclusions of the visit in the Monitoring Visit Report. Follow-up of all issues identified during the visit must be arranged.

After completion of the Monitoring Visit Report, the Study Monitor must send it to the CI/PI and Sponsor within two weeks of the visit taking place. The report will be signed by the Study Monitor and the original will be forwarded to the study file. The Study Monitor will keep a copy of the report.

Where findings have been identified, the CI/PI will be expected to respond within four weeks, detailing corrective and preventative actions and a timescale for completion. These resolutions must be signed by the CI/PI and submitted to the Study Monitor. Any deviations from the aforementioned timescales must be documented.

Issues raised by the Monitor which remain unresolved, or are not actioned in the recommended time frame, must be escalated to the QA Working Group in the first instance and if the issue persists it should be reported to and managed by the R&D Governance Oversight Group for all other sponsored research.

Any significant findings will be presented at the GOG for information.

NB All outstanding issues must be resolved before close-out of the Clinical Trial.

7. DISSEMINATION AND TRAINING

7.1 This SOP and associated templates and forms will be uploaded to the RDE Research website shortly after having been released.

7.2 All staff whose activities are subject to this SOP should ensure that they take time to read and understand the content of this SOP.

7.3 *If applicable, a training log within the Investigator Site File/Trial Master File should be completed to document that members of staff have read and understood the contents of this SOP.*

8. MONITORING COMPLIANCE AND EFFECTIVENESS OF THIS SOP

8.1 In order to monitor compliance with this SOP, the auditable standards will be monitored as follows:

No	Minimum Requirements	Evidenced by
1.	Risk assessments of all Trust Sponsored studies will inform a monitor schedule that outlines which studies require Level 2 and 3 Monitoring.	Review of the R&D Risk Assessment.

2.	The Study Monitor should sign a Monitoring Visit Log.	Evidenced in the ISF/TMF.
3.	The Study Monitor will report all significant findings, deviations, deficiencies, activities, discussions and conclusions of the visit in the Monitoring Visit Report.	Evidenced by reviewing the Monitoring Visit Reports which should be saved in the R&D Monitoring folder (research_develop_admin\Quality Assurance\Auditing&Monitoring), and the ISF/TMF where a copy should be filed.
4.	It should be verified that the correct approved versions of the PIS and Informed Consent Forms were used and that each participant's written Informed Consent was obtained before any study related procedures were performed.	Review of patient notes and MyCare along with the study regulatory documents, Informed Consent Forms and the Monitoring Visit Reports
5.	Where findings have been identified, the CI/PI will be expected to respond within four weeks, detailing corrective and preventative actions and a timescale for completion. These resolutions must be signed by the CI/PI and submitted to the Study Monitor. Any deviations from the aforementioned timescales must be documented.	Relevant correspondence should be saved in the R&D study file and copies of signed reports filed in the ISF/TMF.

8.2 Outcomes from audit will be presented to the R&D Governance Oversight Group (GOG) which will monitor any resulting action plans until all issues have been addressed to satisfaction.

8.3 Issues identified via the audit process which require escalation will be referred to GOG.

9. ARCHIVING ARRANGEMENTS

9.1 The original of this document will remain with the R&D Quality Assurance Coordinator. An electronic copy will be maintained on the R&D section of the Q-Pulse document management system and a pdf copy on the RDE Research website.

9.2 Archive copies must be maintained for any documents which have been superseded. Archive copies in electronic format should be retained indefinitely.

10. REFERENCES

ICH Harmonised Tripartite Guideline for GCP (E6) (http://www.ich.org/)

Health Research Authority (HRA) (http://www.hra.nhs.uk/)

Monitor Responsibilities under ICH GCP

UK Policy Framework for Health and Social Care Research