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JOINT RESEARCH SUPPORT OFFICE

STANDARD OPERATING PROCEDURES

UHL Research Support Office
SOP S-1007 UHL V11 April 2020

Standard Operating Procedure for Management (Monitoring) of research sponsored by University Hospitals of Leicester NHS Trust (UHL)

PCG Reference No: C16/2013

OFFICE BASE

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1. Introduction

This Standard Operating Procedure (SOP) describes the procedures for management of a study site undertaking research sponsored by the University Hospitals of Leicester NHS Trust (UHL) and defines the conduct and frequency of monitoring visits.

The UHL when acting as Sponsor of research has an obligation to ensure that research activity is conducted in accordance with relevant legislation and guidelines.

A Sponsor is required to regularly review the progress of research and to ensure that Investigators comply with the relevant guidelines and legislation appropriate to the individual research activity. It is expected that all Trial Master Files (TMF) and Investigator Site files (ISF) are 'inspection ready' at all times.

The Monitor should act as the main line of communication between the Sponsor and the Investigator. This is achieved through site visits and regular communication to ensure that:

- The rights and well-being of human subjects are protected.
- The reported study data are accurate, complete and verifiable from source documents.
- The conduct of the study is in compliance with the currently approved protocol/amendment(s), with ICH GCP, and/or with the applicable regulatory requirement(s), directives and guidelines and with the applicable version of the Declaration of Helsinki.

2. Scope

This SOP applies to all research sponsored by the UHL

3. Procedures

3.1 Monitoring Plan

The sponsor risk assessment will facilitate the development of the monitoring plan (Appendix 1, 1a).The method of monitoring, the frequency of visits and focus of monitoring visits will be determined by the risk rating allocated to a study to ensure that monitoring approaches are targeted and justified. In addition, the monitoring plan will be further informed with the use of monitoring strategy tables (Appendix 2)

Monitoring of sites may be on site, remote or through central monitoring. Further information with regards to risk rating and the risk assessment process can be found in the sponsor risk assessment SOP S-1003 UHL.

A monitoring plan will be developed for all Clinical Trials of Investigational Medicinal Products (CTIMPS), Non-CE Marked Devices, and for non-CTIMP/ CE marked device studies deemed to be higher risk on a case by case basis.

All monitoring personnel must have evidence of qualification, training and experience.

Where external vendors are providing monitoring as part of the roles and responsibilities e.g. a CTU, the frequency and level of monitoring will be discussed and agreed prior to the study commencing.

3.2 On Site Monitoring

3.2.1 Monitoring Frequency

Monitoring frequency will be discussed with the Chief Investigator (CI) during the initial sponsor review and risk assessment process. Adequate funding provision must be available to provide an appropriate level of monitoring proportionate to the phase, study complexity or anticipated recruitment rate. The experience of the CI and study team will also be taken into consideration.

The first monitoring visit following initiation and study commencement will be determined by the risk level and detailed in the monitoring plan, which should be reviewed at the end of each monitoring visit. If the site does not enroll any patients, or enrolment has stopped, regular monitoring visits will not be scheduled and issues around recruitment discussed with the CI and study team. If there is an extended gap in study activities or a major change in site personnel the monitor will communicate with the CI or PI to ensure site staff are appropriately trained when study activities recommence.

Dose escalation studies

Monitoring visits will be scheduled to ensure that any dose escalation data is monitored prior to any review by data monitoring committees and subsequent dose escalation.

3.3 Remote Monitoring

Remote monitoring may be utilised as a method of maintaining oversight of a study and is considered a part of monitoring whether site visits are taking place or not. These will include regular communication with the site by email or telephone and regular status updates to the Sponsor from the site, regarding recruitment, operational issues such as staff changes, key document amendments, deviations and non-compliances. The content of telephone calls must be documented in writing (Appendix 3) Copies of electronic mail must be kept on file.

3.4 Central Monitoring

Central monitoring may be used in large studies with multiple sites and be managed through a central coordinator. The coordinating centre, will receive information from the investigator sites. Routine visits will not be made unless issues identified trigger concerns.

Central monitoring may consist of remote review of:

- Informed Consent Forms
- Case Report Forms
- A data review etc

Statistical techniques may be employed that allow identification of patterns and trends within large studies.

When using central monitoring, other legislative requirements must also be considered. If documentation with subject identifiers or contact details for telephone follow up/questionnaires are required, a formal system must be in place that complies with the relevant Information Governance legislation (Data Protection Act 2018) and GDPR to ensure access to confidential information is restricted and that subjects of the clinical study are aware that the Sponsor, or third party may have access to their data. This must be explicitly detailed in the subject information sheet/consent form and be approved by the HRA & Research Ethics Committee.

Central monitoring will be discussed as part of the sponsor risk assessment and included in the monitoring plan.

3.5 Triggered Monitoring

Monitoring may trigger a cause for concern, or concerns identified via other means may trigger monitoring. This may require a more in depth assessment of a site, or a review of the risk and revision of monitoring plan. In this case a monitoring visit will be arranged to assess the issues and future monitoring requirements.

Triggers may include concerns over:

- Protocol/Clinical Investigation Plan(CIP) compliance
- Data compliance
- Notably high adverse event rates
- Notably low adverse event rates
- Lower than expected recruitment
- Higher than expected recruitment
- Lack of compliance to regulatory requirements
- IMP management issues
- Drug errors/device user errors

A targeted monitoring strategy will identify sites that require additional support to resolve procedural and compliance issues. Evidence of the subsequent visit or actions based on the trigger must be documented in the TMF and ISF.

4. Preparation for a Monitoring Visit by the Monitor

The Monitor must be familiar with the protocol/CIP, monitoring plan and any relevant Standard Operating Procedures (SOPs). The Monitor will provide adequate notice to the Investigator of an intended visit.
Prior to a monitoring visit, the Monitor must review the following in order to develop a clear list of objectives for the visit:

- Monitoring plan
- Arrange appropriate appointments with support services i.e. Pharmacy/Labs/Tissue bank
- Previous monitoring visit reports if relevant, paying particular attention to any action points recorded.
- Recent correspondence with site
- SAE/SUSAR , SADE/USADE reports, if applicable
- Development Safety Update Report (DSUR)/Annual Safety Report
- Review of approved documents
- Request latest study recruitment figures.

The Monitor will request that all appropriate site staff and required documentation be made available during the visit. Clarification of the documentation required will be provided in written form.

4.1 Preparation for a Monitoring Visit by the Study Team

The CI/PI must make available all files relating to the research activity. This includes the following:

- TMF/ISF
- All consent forms
- All Case Report Forms (CRF)
- Medical notes as requested by the Monitor prior to the visit

5. On-Site Monitoring Visits

5.1 Site and Site Staff Assessment

The Monitor will sign the trial monitoring visit log at every visit (Appendix 4). The date on the log must correspond with those on the monitoring visit report and any follow up correspondence with the site.

A monitoring visit may include the activities listed below however, when applying a risk based approach, it may be necessary to adapt each visit as necessary.

- The Monitor or a Sponsor representative should communicate with the CI/PI and/or delegate at regular intervals to discuss the study status and any issues that may have been identified. The frequency and nature of the communication will be determined by the risk profile.
- Seek assurance that the CI/PI continue to have adequate resources and facilities throughout the study, highlighting where necessary to appropriate organisations i.e. CRN for Support Funding

- Seek assurance from the CI/PI that all site staff involved are qualified for their role within the study and are adequately trained in order to meet the study requirements.
- Check that valid training records, CV's and completed SOP read records exist. Ensure that all site staff have signed, dated and completed the delegation of authority and signature log. Ensuring also that the CI/ PI has countersigned the log.
- Ensure that device accountability (where required) has been undertaken and that the record is complete.
- Confirm that the Investigator and authorised site staff are performing the specified study functions in accordance with the CIP/ protocol and any other written agreement between the Trust and the Investigator / other institution.

5.2 Subject Status and Recruitment Rate

- Review recruitment status at the site.
- Ensure that any barriers or problems with the expected recruitment process are discussed with the PI and documented in the monitoring report.
- Check that all withdrawals of enrolled subjects are reported and explained (where appropriate) in the CRF.

5.3 Informed Consent Procedure

- Ensure that the correct versions of Patient Information Sheets (PIS) and Informed Consent Forms (ICF) are in use. These must be correctly completed and filed appropriately.
- Confirm that no personnel listed on the delegation of authority and signature log have been enrolled.
- Document non-compliance with the correct consent procedure in the monitoring visit report
- Perform consent documentation verification according to the risk profile.

5.4 Adverse Event Review

The Monitor will:

- Review the CRFs and source documents for Adverse Events/Adverse Device Effect
- Ensure current version of Serious Adverse Event (SAE), Serious Adverse Device Effect (SADE), device deficiency reporting form is being utilised. These can be found on the R&I Website
- Determine all SAE/SADE/follow up reports have been reported to the Sponsor & C I. The Monitor must check that SAE/SADEs have been appropriately reported.
- All required SAE/SADE data are recorded in the CRF and consistent with the source data and SAE/SADE form.
- Evidence that expectedness and causality are recorded for all CTIMPs and Non CE Marked Medical Device Studies.
- All documentation is filed in the TMF/ISF and evidence of acknowledgement that all SAEs have been received by the Sponsor.

- Evidence that periodic safety updates and summaries are sent to the competent authority (MHRA) and Ethics Committee as required.

5.5 Protocol Adherence

- Assess the adherence to the protocol and any applicable protocol amendments.
- Ensure that randomisation is being performed in accordance with the protocol and that the blinding is maintained (if applicable).
- Ensure that protocol deviations are reported and any remedial actions are documented in the monitoring visit report, in the CRF (if a comments section has been provided) and in a file note.
- Where applicable report serious breaches as per SOP S-1013 UHL

5.6 Regulatory Compliance

- Ensure that all amendments have been correctly notified to the appropriate statutory and regulatory bodies and copied to the Sponsor and that all necessary favourable opinions/approvals are in place.
- Ensure that all annual reports and DSURs, as appropriate, have been completed and submitted in a timely manner to the correct regulatory bodies.

5.7 Source Data Verification

Monitoring of source data must be verified, agreed and documented in the schedule of source data (Appendix 5) which must be kept in the TMF.

Source data is comprised of records where subject information is first recorded. It includes, but is not limited to, hospital case notes, ECG traces, x-rays, etc.

Confirm that enrolled subjects meet the inclusion / exclusion criteria.
Check that source data records are adequately maintained.
Inform the Investigator of any CRF entry error, omission or illegibility.

Arrangements must be in place for the correction of any errors found in the CRF/eCRF. Errors and inconsistencies in the data recorded may only be corrected by authorised study site personnel as documented in the delegation of authority & signature log. In such cases the responsible person should strike through the incorrect entry with a single line ensuring the original entry remains legible, insert the correct entry immediately alongside and initial and date the change. If there are multiple corrections on a page, each correction should be separately initialed and dated.

- Confirm the accuracy and completeness of data entered into the CRF by comparison with source data and vice versa. Source Data Verification (SDV) will be performed for the following data:
    - Subject ID number and initials
    - Date of written informed consent
    - Subject inclusion / exclusion criteria

- Subject past medical history and demographic data
- Visit dates
- Key efficacy variables
- Adverse Events/ Adverse Device Effects
- Concomitant medications
- Laboratory results
- Other safety and efficacy variables

Where there is a schedule of source data, any items defined as being entered directly into the CRF cannot be verified.

5.8 Drug Accountability

- Review storage conditions of IMP and identify and report any deviation from the requirements of the protocol/Investigator Brochure (IB) (e.g. temperature variations).
- Review expiry dates, stock levels held at site, dispensing and accountability records.
- Check that subject compliance is acceptable, where possible, this should be determined from quantities of returned IMP. Any compliance issues should be brought promptly to the attention of the Investigator.

5.9 Device Accountability

- Review storage conditions of medical device and components and identify and report deviation from the requirements of the IB/ manufacturers instruction for use of all medical devices and components.
- Review component/device exipry dates as applicable and device accountability logs.
- Check that subject/ user compliance is acceptable, Any compliance issues should be brought promptly to the attention of the Investigator

5.9 Randomisation Code Breaks

- Check that there is 24-hour access to the randomisation code breaks (where appropriate)
- In the event of unblinding, the Monitor must check that the reasons for code break are appropriately documented, i.e. the opened code is signed and dated and the treatment/ device assignment and reasons for unblinding are documented in the Subject's medical records and CRF.
- Details of any unblinding, including the reason, must be documented on the monitoring visit report.
- The Monitor must inform the Sponsor within 1 working day of learning of the code break.

5.10 Laboratory / Clinical Procedures

- Check that clinical procedures, sample handling and storage are in accordance with the protocol and laboratory SOPs/policies

- Check that all results are being reviewed, signed and dated in a timely manner by an Investigator and correctly filed. If the result falls outside of normal ranges, clinical significance must be reported.

5.11 Biological Samples (Blood, Tissue, Urine)

- The Monitor will confirm that the protocol requirements have been met regarding timing, storage, shipping and documentation of biological samples.
- Temperature monitoring and recording of stored samples (where applicable)
- Destruction/retention of biological samples

5.12 Trial Master File/Investigator Site File

- Ensure that the TMF/ISF is kept up to date and complete and take action as needed to correct any deficiencies.
- Confirm that all Subjects have been recorded on the subject enrolment / ID log. Confirm that no patient identifiable data is recorded on screening logs.

6. Reporting Timelines

Monitoring visit report forms (Appendix 6/6a and/or Appendix 7) must be completed by the Monitor and submitted to the CI/PI within 21 calendar days of a visit.

The CI/PI will have 28 calendar days to respond to the findings in the using the monitoring visit response document (Appendix 6 and/or appendix 7). If the monitoring response document has not been received, a reminder will be sent giving the CI/PI a further 14 days to respond. Failure to respond after the reminder will result in the non-compliance SOP S-1016 UHL being implemented at a minimum of a major finding.

Monitoring visit reports will be escalated within 5 working days if non-compliance and/or areas of concern have been identified in accordance with the non-compliance SOP S-1016 UHL. All actions required will be followed up until resolution. All discrepancies that cannot be resolved will be documented in a file note and signed by the CI/PI, relevant site staff and Monitor.

7. Non CTIMP/ CE Marked Device/ proof of concept study Monitoring by the Study Team

As the UHL operates a risk based monitoring programme for non-CTIMP/ CE Marked Device/Proof of Concept studies, not all sponsored studies or every non-CTIMP/ CE Marked/Proof of Concept Device study site can be monitored by the Sponsor. Remote monitoring by the study team may be undertaken by utilising the Sponsor Non-CTIMP interim site monitoring checklist (Appendix 8/8a). This will enable Sponsor/CI over sight and ensure that collaborating site ISF are reflected in the TMF.

The checklist should be utilised at time points throughout the study dependent on study timeline and Sponsor requirement. The checklist may also be utilised should a triggered monitoring event occur.

8. Monitoring of External Vendors

External vendors will be visited as stated in the external vendor selection SOP S-1032 UHL.

9. Responsibilities

	Responsibility	Undertaken by	Activity
1.	Sponsor	Monitor	Establish a clear list of objectives prior to each monitoring visit.
2.	Sponsor	Monitor	Request that all site staff and documentation required are available for the monitoring visit.
3.	Sponsor	Monitor	Ensure that as appropriate the objectives of a monitoring visit are met by following the procedures in section 3.
4.	Sponsor	Monitor	Complete all appropriate documentation as detailed in section 3
5.	Sponsor	Monitor	Define frequency of monitoring visits and CRF collection schedule
6.	Sponsor	Monitor	Review the monitoring visit report and initiate any necessary actions
7.	CI/PI	CI or delegate	Complete monitoring visit report response and return within 28 calendar days detailing action taken and planned.
8	Sponsor	Monitor	Follow up on monitoring visit report response requesting update of outstanding corrective action.

10. Legal Liability Statement

Guidelines or Procedures issued and approved by the Trust are considered to represent best practice. Staff may only exceptionally depart from any relevant Trust guidelines or Procedures and always only providing that such departure is confined to the specific needs of individual circumstances. In healthcare delivery such departure shall only be undertaken where, in the judgement of the responsible healthcare professional it is fully appropriate and justifiable – such a decision to be fully recorded in the patient's notes and in the research site file.

11. Monitoring and Audit Criteria

Key Performance Indicator	Method of Assessment	Frequency	Lead
All research sponsored by UHL has appropriate Risk Assessment	Included in the monitoring / audit programme.	Random audits / monitoring conducted according to Risk profile of research activity.	Head of Research Operations or their Delegate

This table is used to track the development and approval of the document and any changes made on revised / reviewed versions

DEVELOPMENT AND APPROVAL RECORD FOR THIS DOCUMENT		
Author / Lead Officer:	Carolyn Maloney / Julie James	**Job Title:** Head of Research Operations / Clinical Trials Monitor
Reviewed by:	UHL R&I Management Meeting	
Approved by:	Professor Nigel Brunskill	**Date Approved:** 1/10/20

REVIEW RECORD			
Date	**Issue Number**	**Reviewed By**	**Description Of Changes (If Any)**
Oct 2013	2	Carolyn Maloney	Version 1 revised following review of Sponsor Processes
March 2014	3	Carolyn Maloney	Version 2 amended to clarify reporting requirement timelines, now version 3
April 2015	4	Carolyn Maloney	Version 3 amended to reflect new logo and corporate identity. Now version 4
May 2015	5	Carolyn Maloney	Version4 amended to update appendices, add reference to dose escalation studies and minor amendment to responsibility table.
Sept 2015	6	Carolyn Maloney	Version 5 amended to update appendices and change the name of the response document
August 2016	7	CM, LW, JJ	HRA additions. Adding section numbering & monitoring for Non-Ctimp.
November 2017	8	CM, MM	Review for proportionality and emphasis on Risk Adaptation
January, September, December 2018	9, 10	CM,JJ,CL JJ	Logos updated. Version numbers out of sync, updated to reconcile version numbers with existing docs & review record. V9 review completed in Jan 2018 but not recorded on Review Record Updated to include CE and Non-CE marked Medical Device Studies Appendix 1a, 6a, 8a created to cover Medical Devices
April 2020	11	LW,JJ AM	Consistency review

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