



**UNIVERSITY OF LEICESTER, UNIVERSITY OF LOUGHBOROUGH
&
UNIVERSITY HOSPITALS OF LEICESTER NHS TRUST
JOINT RESEARCH SUPPORT OFFICE
STANDARD OPERATING PROCEDURES**

**University of Leicester (UoL) Research Governance Office
SOP S-1007 UoL**

Version 6, November 2016

**Site Management (Monitoring) for
University of Leicester when Acting as Sponsor**

OFFICE BASE

Research Governance Office
Research & Enterprise Division
University of Leicester
Fielding Johnson Building
University Road
Leicester
LE1 7RH

Effective Date: April 2017



1 Introduction

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

The University of Leicester when acting as Sponsor of research has an obligation to ensure that research activity is conducted in accordance with the 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 UoL.

3 Procedures

3.1 Monitoring Plan

The Sponsor Risk Assessment will facilitate the development of the Monitoring Plan ([Appendix 1](#)). The method of monitoring, the frequency and focus of monitoring visits will be determined by the risk rating allocated 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 UoL](#).

A monitoring plan will be developed for all CTIMP clinical trials and for non-CTIMP trials on a case by case basis. The UoL will operate a risk based audit programme of non-CTIMP studies, and will aim to monitor 10% of interventional non-CTIMP studies per annum.

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

3.2 Monitoring Frequency

Monitoring frequency will be discussed with the Chief Investigator (CI)/Principal Investigator (PI) at the initial Sponsor review and risk assessment. Adequate funding provision must be available to provide appropriate levels 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 trial commencement should occur within four (4) weeks of enrolment of the designated number of subjects detailed in the monitoring plan. 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 trial activities or a major change in site personnel the monitor will communicate with the CI to ensure that site staff are appropriately trained when trial activities recommence.

Monitoring visits should 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 site 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 6](#)). 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

It may also employ statistical techniques that allow identification of patterns and trends within large trials.

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 [Data Protection Act 1998](#) to ensure access to confidential information is restricted and that subjects of the clinical trial 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 and 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. 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/audit visit will be arranged to assess the issues and future monitoring requirements.

Triggers may include concerns over:

- Protocol 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.

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 trial master file and investigator site file.

3.6 Preparation for a Monitoring or Audit Visit by the Monitor

The monitor must be familiar with the protocol, monitoring plan and any relevant Standard Operating Procedures (SOPs). The monitor will provide adequate notice to the Investigator.

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 reports, if applicable
- DSUR/Annual 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.

3.7 Preparation for a Monitoring or Audit Visit by the Study Team

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

- Trial Master File/Investigator Site File.
- All consent forms
- All Case Report Forms
- Medical notes as requested by the monitor prior to the visit.

3.8 On-Site Monitoring Visits

3.8.1 Site and Site Staff Assessment

The monitor will sign the Trial Monitoring Visit Log at every visit ([Appendix 3](#)). The date on the log must correspond with those on the monitoring visit report and any follow up correspondence with the site.

Procedures required during monitoring visits are listed below. In the event that the monitor is unable to meet these requirements, for any reason, the monitor must inform the Sponsor at the earliest opportunity and discuss with the Investigator where appropriate.

- The monitor must meet with the Chief / Principal Investigator (CI/PI) and/or delegate at regular intervals during the study to discuss the study status and any issues that have been identified.
- Verify that the CI/PI has adequate resources and facilities throughout the study
- Ensure that all site staff involved in the study are qualified for their role within the study and are adequately trained in order to meet the study requirements.
- Check GCP certificates, CV's and SOP read Records.
- Ensure that all site staff have provided a signed and dated current CV and have completed the Delegation of Authority and Signature Log. Ensure that the PI has countersigned the log.
- Assess whether any changes in facilities or site staff will influence the conduct of the study at site, and if so, discuss with the Investigator, as appropriate.
- Verify that the Investigator and authorised site staff are performing the specified study functions in accordance with the protocol and any other written agreement between the Trust and the Investigator / other institution.

3.8.2 Subject Status and Recruitment Rate

Review the target recruitment rate and subject status at the Centre. Any significant deviations from the estimated recruitment rate, and how they may be rectified, should be documented in the monitoring report and discussed with the Sponsor. All withdrawals of enrolled subjects are reported and explained in the Case Report Forms (CRF).

3.8.3 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 100% consent verification for all UoL Sponsored CTIMP studies as directed since 2011.

3.8.4 Adverse Event Review

The monitor will:

- Review the CRFs and source documents for Adverse Events.
- Ensure current version of Serious Adverse Event (SAE) reporting form is being utilised. These can be found on the College Website, [Research Governance Pages](#).
- Determine all SAEs/follow up reports have been reported to the Sponsor/Chief Investigator/Research Ethics Committee and Research

Governance Office as required by UK regulations. The monitor must check that this form has been completed and signed by the Principal Investigator/Co-Investigator and returned to the Research Governance Office within 24 hours of the team becoming aware of the event.

- All required SAE data are recorded in the CRF and consistent with the source data and SAE form.
- Evidence that Expectedness and Causality are recorded for all Clinical Trials of Investigational Medicinal Products (CTIMP).
- All documentation is filed in the Trial Master File/Investigator Site File 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.

3.8.5 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 UoL Reporting Serious Breaches](#).

3.8.6 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 development safety update reports, as appropriate, have been completed and submitted in a timely manner to the correct regulatory bodies.

3.8.7 Source Data Verification

Monitoring of source data should be verified as agreed and documented in the source data agreement ([Appendix 4](#)) which should 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.

- Verify 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. 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.

- Verify 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
 - Concomitant medications
 - Laboratory results
 - Other safety and efficacy variables

Where there is a Source Data Agreement, any items defined as being entered directly into the CRF cannot be verified.

3.8.8 Drug Accountability (CTIMP only)

- Review storage conditions of investigational medicinal product and identify and report any deviation from the requirements of the Protocol/Investigator Brochure (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 where identified. Any compliance issues should be brought promptly to the attention of the Investigator.

3.8.9 Randomisation Code Breaks

- Check that there is 24-hour access to the randomisation code breaks.
- In the event of unblinding, the monitor must check that the reasons for code break are adequately documented by the Investigator, i.e. the opened code is signed and dated and the treatment 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.

3.8.10 Laboratory / Clinical Procedures

- Check that clinical procedures, sample handling and storage are in accordance with the protocol.
- 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 in line with the monitoring plan.

3.8.11 Biological Samples (Blood, Tissue, Urine)

- The Monitor will verify 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)

3.8.12 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.
- Verify that all subjects have been recorded on the Subject Enrolment / ID Log. Verify that no patient identifiable data is recorded on screening logs.

4 Reporting Timelines

Monitoring Visit Report forms ([Appendix 5](#) and [Appendix 7](#)) must be completed by the monitor and submitted to the Investigator within 21 calendar days of a visit. The Principal Investigator will have 28 calendar days to respond to the findings in the format of Monitoring Visit Response Document. If the Monitoring Report Response Document ([Appendix 5](#) and [Appendix 7](#)) 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](#) being implemented at a minimum of a major finding.

Monitoring Visit Reports will be escalated to the Sponsor within 5 working days if non-compliance and/or areas of concern have been identified for escalation in accordance with the [non-compliance SOP S-1016](#). 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 PI, relevant site staff and Monitor.

5 Non CTIMP Monitoring by the Study Team

As the UoL operates a risk based audit programme for non-CTIMP studies, not all sponsored studies or every non-CTIMP study centre can be audited by the Sponsor. Remote monitoring by the study team may be undertaken by utilising the Sponsor Non-CTIMP Interim Site audit Checklist ([Appendix 7](#)). This will enable the

Sponsor/Chief Investigator oversight and ensure that collaborating centres' Investigator Site Files reflect the Trial Master File.

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.

6 Monitoring of External Vendors

External Vendors will be visited as stated in the External Vendor Selection SOP.

7 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 all objectives of a monitoring visit are met by following the procedures as pre-defined in section 2.
4	Sponsor	Monitor	Complete all appropriate documentation as detailed in section 2.
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	Sponsor	CI or delegate	Complete the Monitoring Visit Report Response Document and return within 28 calendar days detailing action taken and planned.
8	Sponsor	Monitor	Follow up on the Monitoring Visit Report Response Document requesting update of outstanding corrective action.

8 Monitoring and Audit Criteria

Key Performance Indicators	Method of Assessment	Frequency	Lead
All research sponsored by UoL has appropriate Risk Assessment	Included in the monitoring / audit programme.	Random audits / monitoring conducted on 10% of research activity.	Research Governance Manager or their Delegate

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

9 Development and approval Record for this document

Author / Lead Officer:	Wendy Gamble
Job Title:	Research Governance Manager
Reviewed by:	UoL Research Management and Operations Group (RSMOG)
Approved by:	Professor Nigel Brunskill 
Date Approved	10/04/2017

10 Review Record

Date	Issue Number	Reviewed By	Description Of Changes (If Any)
Oct 2013	2	Wendy Gamble	Version 1 revised following review of Sponsor Processes
March 2014	3	Wendy Gamble	Version 2 amended to clarify reporting requirement timelines, now version 3
June 2015	4	Wendy Gamble	Version 3 amended to update appendices, add reference to dose escalation studies and minor amendment to responsibilities table.
March 2016	5	Diane Delahooke	V4 amended to include non CTIMP monitoring/audit checklist.
Nov 2016	6	Diane Delahooke	HRA additions, corrections to numbering.

11 Distribution Record

Date	Name	Department	Received