




SOP Number 012
SOP Title Monitoring

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1. PURPOSE

The purpose of this Standard Operating Procedure (SOP) is to describe the procedures for monitoring clinical trials.

2. INTRODUCTION

Monitoring verifies that:

- The rights and well-being of the human subjects are protected
- The reported trial data are accurate, complete, and verifiable from source documents
- The conduct of the trial is in compliance with the currently approved protocol/amendment(s), standard operating procedures (SOPs), GCP, and the applicable regulatory requirements.

Monitoring is an integral process in the quality control of a clinical trial and is designed to verify the quality and integrity of the study. Monitoring may take place centrally, at site, or a combination of the two, depending on the assessment of risk within the study, which may be defined in a formal Risk Assessment document.

3. SCOPE

The scope of this procedure is for all clinical trials sponsored by the University of Oxford, but may also be used for other research studies at the discretion of the unit.

4. DEFINITIONS

Monitor

A suitably qualified, trained and experienced individual responsible for overseeing the progress of a clinical trial by means of monitoring. The Monitor should be independent of the study team.

Monitoring

The process of ensuring that a clinical trial is conducted, recorded and reported in accordance with the protocol, standard operating procedures (SOPs), Good Clinical Practice (GCP), and relevant regulatory requirements. This may include activities undertaken by trial oversight committees, e.g. TMG, DMC, TSC (see 6.3 below).

Monitoring Plan

A trial-specific and risk-based plan outlining monitoring content, procedures, communication plan and frequency during the trial.

Monitoring Report

A written report generated following any significant monitoring activity.

Site Monitoring

Any interaction between the monitor and the site, whether it be by physical visit or through other means of communication.

Central Monitoring

Monitoring of trial data and documents which takes place remotely from the investigative site. Trial data may include both clinical data and data relating to the management of the study (e.g. participant enrolment rates, safety reporting rates).

Source Documents/Data

Source documents are the original location where data are first recorded (e.g. hospital records, data recorded directly from automated instruments). Case Report Forms may also be considered as source documents where this is the location in which data are first recorded.

Source Data Verification

The process by which information recorded for a study is verified against source documents and data.

Case Report Form (CRF)

A printed, or electronic (eCRF) document designed to record all of the protocol-required information about trial participants.

Oversight Committee

An independent group of experts assessing the progress and safety data of a clinical trial.

End Point Review

An independent, where appropriate blinded, expert review of a particular data point (e.g. primary outcome measure) within a clinical trial (see section 6.2 for examples).

Risk Assessment

The identification, evaluation and estimation of the levels of risks involved in a situation.

5. RESPONSIBILITIES

Sponsor (these responsibilities may be delegated in a written agreement)

- Review risk assessment for the study
- Ensure a Monitoring Plan is produced
- Review Monitoring Plan
- Oversee monitoring activities for the study

Chief Investigator (CI) or Delegate

- Create risk assessment for the study
- Review and agree the study Monitoring Plan
- Facilitate monitoring access for the study in terms of TMF, data, IMP, and IMP management
- Receive Monitoring Reports
- Act on any issues identified in the monitoring report, as appropriate
- Respond to Monitor requests for completion/correction of data and provision of essential documents
- Coordinate trial management information to facilitate central and/or site monitoring

Monitor

- Comply with the study Monitoring Plan
- Produce appropriate written Monitoring Reports in a prompt manner
- Maintain their training record to demonstrate appropriate level of knowledge

6. SPECIFIC PROCEDURE

6.1 Risk Assessment in Clinical Trials

A risk assessment for a clinical trial should be agreed between the Sponsor and the Chief Investigator. This should include an evaluation of risks to both participant (e.g. comparison to standard care etc.) and the study (e.g. database design, IMP supply and recruitment rate etc.), and include measures to be undertaken to mitigate the risks (e.g. level of monitoring). Studies deemed to be high-risk may require extensive site monitoring, whilst low-risk studies may appropriately employ more, or even exclusively, central monitoring.

6.2 Monitoring Plan

A Monitoring Plan should be agreed between the Sponsor and the Chief Investigator, detailing monitoring content, procedures, frequency, and communication plans, and which takes account of the risk assessment undertaken. Source data for the study, and source data verification with the CRF will be defined. Monitoring should be proportionate to the objective, design, size, complexity, blinding and endpoints associated with the study. Where specialised expertise or knowledge is required to review data (e.g. laboratory or imaging analysis) an independent, where appropriate blinded, end point review should be considered.

Monitoring plans may include elements of both central and site monitoring as appropriate, and should be reviewed at initiation, during and at the end of the study in terms of relevance and effectiveness, and filed in the TMF.

6.3 Oversight Committees

Large and/or complex studies will benefit from the establishment of one or more oversight committees, for example: -

- Trial Management Group (TMG)
This would include those who are responsible for day-to-day management of the study, and will monitor all aspects of conduct and progress, including protocol compliance and study quality.
- Data Monitoring Committee (DMC)
To review the accruing study data at intervals to monitor the study, safety data, and critical efficacy endpoints.
- Trial Steering Committee (TSC)
To provide overall supervision of the study to ensure it is conducted according to the principles of GCP and relevant regulations. It should agree the protocol and any amendments, and provide advice to investigators on all aspects of the study.

A decision as to what oversight committees need to be in place will be made before the trial begins, and this will be documented. Oversight committee reports should be produced, and filed in the TMF.

6.4 Central Monitoring

Centralised procedures can be used to confirm patient eligibility, corroborate the existence of the patient, and to check missing or invalid data.

A range of techniques, including statistical, may be useful for large, multicentre studies where unusual patterns of data may be identified, showing perhaps sites or individuals where there may be deviation from the protocol.

Trigger points should be defined in the monitoring plan, which will identify requirements for further action, including training and targeted site monitoring, where appropriate. However, other situations may arise that also require further action.

Central monitoring should be documented, reported, and filed in the TMF.

6.5 Site Monitoring

Where site monitoring is to be undertaken, there should be clear instructions outlining the purpose, responsibilities and procedures.

The Monitor should generally review participant eligibility, informed consent, data relating to study outcome variables, and safety recording and reporting, in addition to IMP accountability and storage, according to the Risk Assessment and the Monitoring Plan. The TMF should be checked to ensure it is accurate, current and complete, and demonstrates Investigator oversight of the study (e.g. meeting minutes).

6.6 Monitoring Reports

Following each type of Monitoring Visit or associated activity, a report will be produced detailing what has been observed and discussed during the visit. The Monitoring Report will be reviewed by the Sponsor or delegate, and will be filed in the TMF. The site will be made aware of any issues or actions required.

Monitoring reports, whether central or site, should be produced without undue delay to allow prompt review by the Sponsor or delegate, thus aiding early identification of issues.

6.7 Findings Resolution

The Monitor should contact the study staff between monitoring visits to follow-up on the progress of action points and to provide clarification as needed. The Monitor should ensure all action points are completed and / or carried over to the next monitoring visit or associated activity. Any unresolved findings should be escalated appropriately. Subsequent monitoring reports should document when all outstanding findings have been resolved.

7. RELATED DOCUMENTS

University of Oxford Core SOP 002 Protocol Development
University of Oxford Core SOP 003 Safety Reporting for CTIMPs
University of Oxford Core SOP 006 Trial Master File
University of Oxford Core SOP 005 Archiving of Essential Documents

8. REFERENCES

Research Governance Framework For Health And Social Care, 2005
MRC/DH/MHRA Joint Project Risk-adapted Approaches to the Management of Clinical Trials of Investigational Medicinal Products, 10th October 2011

9. CHANGE HISTORY

Version No.	Effective Date	Significant Changes	Previous Version No.
2.0	See page 1	Changes to the front page and scope to align with updated core SOP template. Added examples to the risk assessment section, added section 6.7 on finding resolution and added end point review in the monitoring plan section.	1.0