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Standard Operating Procedure: MONITORING

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Standard Operating Procedure: Monitoring

PURPOSE

To describe the responsibilities and procedures for monitoring a clinical trial conducted by the TCC.

INSTITUTIONAL SOP POLICY

All SOPs produced for the TCC must be produced in conjunction with LSHTM policies and procedures.

BACKGROUND

Monitoring is the act of overseeing the progress of a research study. The purpose of monitoring is to verify that:

• The rights and well-being of participants are protected.
• The reported study data are complete, accurate and verifiable.
• The study is conducted, recorded and reported in compliance with the currently approved protocol/amendment(s), ICH-GCP [1] and any applicable regulations or guidelines.

Definitions

Case Report Form (CRF) – A printed, optical or electronic document designed to record all of the protocol-required information to be reported to the sponsor on each trial participant.

Source Documents - Original documents, data and records. Source documents are the first place where data are recorded. The CRF may be source for some trial data (i.e. data may be recorded directly onto CRFs with no prior written or electronic record of data). The study protocol should document the identity of any data recorded directly onto the CRFs.

Source Data Verification (SDV) – The process by which information reported by an investigator or authorised site personnel is compared with source documents to ensure that it is complete, accurate & verifiable.

Hazard – Anything that could cause harm. This includes hazards to the participant, hazards to the research, hazards to the organisation or hazards to the researcher.

Risk – Probability that harm will be caused by the hazard.

Investigational Medicinal Product (IMP) - a pharmaceutical form of an active substance or placebo being tested, or to be tested, or used, or to be used, as a reference in a clinical trial. This includes a medicinal product that has a marketing authorisation but is, for the purposes of the trial:

- used or assembled (formulated or packaged) in a way different from the form of the product authorised under the authorisation or

- used for an indication not included in the Summary of Product Characteristics (SPC) under the authorisation for that product or
- used to gain further information about the form of that product as authorised under the authorization.

SCOPE

This SOP applies to all personnel within the TCC who are involved in a clinical trial requiring monitoring and who have monitoring responsibilities in a trial.

RESPONSIBLE PERSONNEL

- Trials conducted by the TCC for which LSHTM is the Sponsor will require that the TCC carry out the monitoring responsibilities delegated to the Chief Investigator if he/she is part of the TCC team. The TCC on behalf of the LSHTM has responsibility for ensuring trials are adequately monitored [2,3].
- The TCC should determine/agree the extent and nature of monitoring appropriate for a particular study.
- The TCC may appoint a "monitor", particularly where site monitoring is required.
- Monitors should be appropriately trained and should have the scientific and/or clinical knowledge needed to monitor the trial adequately. It is recommended that any relevant training, education or experience of monitoring be documented. The International Conference on Harmonisation GCP (ICH/GCP) provides further guidance on the responsibilities of a monitor [1].

PROCEDURE

Monitoring plan

Planned monitoring procedures for a research study should be clearly documented within a monitoring plan (details may be included within the protocol or as a separate document). The monitoring plan should demonstrate how the TCC intends to meet responsibilities for ensuring compliance of sites with currently approved protocol/ amendment(s), GCP and any applicable regulations or guidelines.

The monitoring plan should ideally include:

- The responsibilities of those involved in monitoring a study.
- The extent and nature of monitoring to be employed (including frequency of monitoring procedures, level of central/site review and detail/location of any source documentation).
- Procedures for documenting monitoring visits and dealing with any issues raised.

Determining the Extent & Nature of monitoring

The extent and nature of monitoring should be determined/agreed by the TCC, prior to the start of the study. This will be based on considerations such as the objective, purpose, design, complexity, blinding, size and endpoints of the study [1].

The TCC may find it useful to carry out a study risk assessment to determine the intensity and focus of monitoring activity. The TCC procedure for risk assessment is located in [TCC SOP 029] and further guidance on performing a risk assessment is provided by the MRC/DH joint project [4, 5]. The risk assessment should consider the potential hazards of a study and determine the likelihood and impact of each hazard. Consideration should be given to minimising any potential risks.

The MRC/DH joint project suggests key areas to consider when establishing appropriate monitoring procedures for a particular study [6]. Example trial scenarios are also provided with suggested approaches to monitoring in relation to risk [7].

Types of monitoring

There are a number of different methods of monitoring a study. A combination of one or more of the following methods may be adopted, depending on the risk associated with a particular study:

Trial Oversight Committees: The TCC requires that all studies it conducts will have some oversight committees including a Protocol Committee/Trial Management Group (TMG), Trial Steering Committee (TSC) and a Data Monitoring Committee (DMC).

Central monitoring: Information available at the main trial office may allow a degree of central monitoring. This could include review of trial data for omissions, inconsistencies or invalid information; verification of consent, eligibility or outcome data; verification of participant existence; review of recruitment rates, withdrawals and losses [6, 7]. Central statistical monitoring techniques may be used to compare data from different sites to identify sites that may warrant further investigation or site monitoring [8].

Site monitoring: A degree of on-site monitoring may be required, whereby a monitor will visit participating sites to review trial conduct and data collection. Site monitoring may be used for a variety of purposes, including review of essential site documentation, source data verification and ongoing training of site staff [6]. At each site visit, the monitor should continually review the acceptability of site personnel, facilities and trial progress.

Source Data Verification: 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 trial data should be in agreement with the information they contain [6]. Checking original documentation also confirms the identity and existence of each participant.

Site or even central monitoring may involve source data verification on a minimum percentage of trial data, or directed to more critical data for a particular trial, such as consent, eligibility or endpoint data and/or serious adverse events. The monitoring plan should document what source documentation will be available for a particular study, where this is located and the requirements for SDV.

Monitoring reports

Monitoring visits and other monitoring procedures should be documented. This is normally in the form of a written report, documenting the visit date, site, name of monitor, name of investigator (or other individuals contacted), summary of what the monitor reviewed, any significant findings/facts, deviations and deficiencies, conclusions, actions taken or to be taken and/or actions to secure compliance [1]. It should be clear who reviews the monitoring reports.

Follow-up to monitoring

Monitoring may provide important feedback on common problems associated with a particular study. The outcome of monitoring can be very useful in determining the focus for further site training.

It should be clear how feedback from monitoring procedures is provided to the trial sponsor, site staff and other relevant bodies.

For clinical trials of Investigational Medicinal Products (IMPs), the TCC on behalf of the sponsor should also consider requirements for notifying the MHRA of any serious breaches of compliance [9].

Any issues or concerns raised at on-site monitoring visits should ideally be discussed locally with relevant study staff.

REFERENCES

1. ICH Harmonised Tripartite Guideline for Good Clinical Practice (1996), accessible at: http://www.ich.org/LOB/media/MEDIA482.pdf

2. Medicines for Human Use (Clinical Trials) Regulations 2004, Schedule 1, Part 2 (http://www.uk-legislation.hmso.gov.uk/si/si2004/20041031.htm)

3. "Department of Health Research Governance Framework for Health & Social Care" http://www.dh.gov.uk/prod_consum_dh/groups/dh_digitalassets/@dh/@en/documents/digitalasset/dh_4108965.pdf

4. MRC/DH joint project. Workstream 4: Trial Management and Monitoring A) Clinical Trial Risk Assessment
http://www.ct-toolkit.ac.uk/_db/_documents/Trial_RA.pdf

5. MRC/DH joint project. Management of a portfolio of Trials 2: Assessment of risk.
http://www.ct-toolkit.ac.uk/_db/_documents/MPTrials2.pdf

6. MRC/DH joint project. Workstream 4: Trial Management and Monitoring C) Monitoring Procedures
http://www.ct-toolkit.ac.uk/_db/_documents/Trial_MP.pdf

7. MRC/DH joint project. Trial Scenarios.
http://www.ct-toolkit.ac.uk/trial_scenarios.cfm

8. M Buyse, SL George, S Evans, et al. for the International Society for Clinical Biostatistics. Subcommittee on Fraud. The role of biostatistics in the prevention, detection and treatment of fraud in clinical trials. Statist Med 1999;18:3435-51.

9. MHRA Guidance for the notification of serious breaches of GCP or the trial protocol. http://www.mhra.gov.uk/Howweregulate/Medicines/Inspectionandstandards/GoodClinicalPractice/index.htm

REFERENCED GUIDES/SOPS

TCC SOP 029 Risk Assessment of a Clinical Trial
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APPENDICES

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