Monitoring Clinical Trials

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1. PURPOSE

The purpose of this Standard Operating Procedure (SOP) is to describe the monitoring procedures for clinical trials sponsored by Imperial College Academic Health Science Centre (AHSC).

2. INTRODUCTION

Monitoring is defined in The International Conference on Harmonisation of Good Clinical Practice (ICH GCP) guidelines as:

“The act of overseeing the progress of a clinical trial, and of ensuring that it is conducted, recorded, and reported in accordance with the protocol, SOPs, GCP, and the applicable regulatory requirement(s), ICH GCP, section 1.38”

Section 5.18 of ICH GCP states in detail the minimum requirements for monitoring of clinical trials.

The purpose of monitoring is to verify 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), with GCP, and with the applicable regulatory requirements.

Monitoring is an integral role in the Quality Control (QC) of a clinical trial and is designed to verify the quality of the study. Audits are designed to assess and assure the reliability and integrity of a trial’s quality control systems and are a way of measuring performance against recognised standards (Quality Assurance or QA). For further information on audits, consult JRCO/SOP/018.

Monitoring is usually performed by the JRCO monitors, an appropriately trained member of the study team/trial coordinating centre or by a contracted external monitor and should be designated on the study delegation log.

The involvement of Contracted External Monitor(s), the JRCO monitors, and the CI or PI in monitoring the AHSC sponsored CTIMP studies will depend on whether the study is taking place in the AHSC hospitals, the College associated NHS Trusts or outside both the AHSC sites and the College associated NHS Trusts.

The AHSC sites comprise of:
- Charing Cross Hospital;
- Hammersmith Hospital;
- Queen Charlotte’s and Chelsea Hospital;
- St Mary’s Hospital and
- Western Eye Hospital.

While the College associated NHS Trusts are:
- Royal Brompton and Harefield NHS Trust;
A Contracted External Monitor is defined in this context as any individual qualified by training and experience and who is not employed by the JRCO, AHSC but is contracted to carry out clinical research monitoring in accordance with the GCP principles [see monitoring definition above].

3. PROCEDURE

3.1 Qualification of monitors

Monitors should be appropriately trained, and should have the scientific and/or clinical knowledge needed to monitor the trial adequately. A monitor’s qualifications should be documented. Training records, including relevant qualifications, should be kept by the monitor and checked by the Chief Investigator. For further information on training records, see JRCO/SOP/024.

The monitor should be familiar with the Investigational Medicinal Product (IMP), the protocol, information sheet and consent form, as well as the Imperial College AHSC SOPs, GCP and applicable regulatory requirements.

3.2 Types of monitoring

3.2.1 Coordinating Centre day-to-day monitoring

Day-to-day monitoring should be carried out by those responsible for running the study. This would normally include the following checks:

- Data collected are consistent with the protocol
- The case report forms (CRFs) are only being completed by authorised staff
- No key data are missing
- Data appears to be valid (e.g. within range and is consistent)
- A review of recruitment rates, withdrawals and losses to follow-up

3.2.2 Central Monitoring

Centralised procedures can be used to confirm patient eligibility (usually through the collection of pathology reports to substantiate a diagnosis), to corroborate the existence of the patient (for example, through The Office for National Statistics (ONS) flagging or collection of an imaging investigation) and to determine the outcome (for example, ONS flagging for survival end-points or central assessment of the results of an investigation, such as a X-ray or scan).

In large, multi-centre trials, central monitoring of data using statistical techniques is particularly useful for the early identification of:

- Unusual patterns or trends
- Issues with plausibility or consistency
- Safety signals
other deviation from the protocol/trial requirements such as poor/late completion of CRFs.

Where centralised monitoring indicates problems, it can be used to efficiently direct on-site monitoring activities to those sites requiring further investigation and/or additional training support. Although omissions (e.g. failure to report a serious adverse event (SAE)) or data entry errors cannot be detected directly, it may be possible to compare data from the different sites to identify sites that warrant investigation.

Examples of central statistical monitoring checks include:

1. Missing or invalid data
   Range checks can be used to identify unlikely or implausible values, such as extreme values for weight, or diastolic greater than systolic blood pressure. For trials using electronic data capture methods, these checks can usefully be built into the data collection form; any such automatic safeguards should be validated to ensure that they function correctly.

2. Calendar checks
   Examining the day of the week that patients were randomised can be revealing (e.g. randomisation on Sunday in a trial of patients attending outpatient clinic). It is also helpful to compare the order of trial forms (particularly if they have an ordered numbering system) with the dates they were completed.

3. Unusual data patterns
   Data from one site can be compared with data for the trial as a whole to identify patterns such as digit preference, rounding, or unusual frequency distribution (e.g. mean, variance, skewness). Such checks can be applied both to a single variable (e.g. systolic blood pressure) and to the joint distribution of several variables (e.g. systolic blood pressure and weight).

4. Rates of reporting
   The frequency of reported adverse events and of missing data can be compared between centres.

5. Repeated measures
   Where the same variable is measured on multiple occasions for each participant during the trial, it is possible to check that the variability and within individual changes of such repeated measurements is broadly consistent with the pattern seen for the trial as a whole.

6. Comparison with external sources
   Checks with birth and death registries or with disease-specific registries (e.g. cancer registry) can be used to identify that particular patients exist and that particular events have (or have not) occurred.
In applying all these checks it is important to recognise that some variability is to be expected. Data that are too good should raise suspicion in the same way as data that are unusually poor.

3.2.3 On-site monitoring
On-site monitoring visits may be used in a variety of different ways:
- to educate staff about the trial; review understanding of the protocol and trial procedures;
- to verify that the staff at the site have access to the necessary documents to conduct the trial;
- to ensure that the required pharmacy and laboratory resources are adequate;
- to check adherence to the protocol and GCP by reviewing such things as signed consent forms and patient eligibility,
- to verify all protocol required data (e.g. adverse event/concomitant medication) have been recorded on the CRFs and compared with data in the clinical records to identify errors of omission as well as inaccuracies.
- To check trial procedures (e.g. informed consent procedures, data collection, CRF completion) to ensure quality and consistency and confirm all assessments are being made by appropriately qualified staff;
- To identify staff training needs.

3.3 Extent of monitoring
The sponsor should ensure that the trials are adequately monitored and determine the appropriate extent and nature of monitoring. This should be based on the objective, purpose, design, size, complexity, blinding, endpoints and risks associated with the clinical trial a CTIMP study is assessed as “high risk” or is First in Mankind which is automatically considered to be “high risk” the JRCO monitor will agree the frequency of routine monitoring visits with the CI of the study.

3.3.1 Risk Assessment
Appendix 1 contains an example risk assessment form that can be used by CI's to suggest the appropriate level of monitoring for your study and to identify risks that may not have been considered in protocol development.

In general, for most studies there will be a need for on-site monitoring, however, in some academic clinical trials, the CI in conjunction with the JRCO, may decide that central monitoring alongside relevant training and meetings with extensive written guidance can assure appropriate conduct of the trial. The JRCO will conduct a separate risk assessment as part of its study set-up process and will advise the CI on the recommended level of monitoring.
3.4 Monitor’s responsibilities
Monitors, in accordance with the Sponsor’s requirements, should ensure that the trial is conducted and documented properly by carrying out as a minimum the following activities:
- Ensuring that data collected is consistent with adherence to the protocol
- Case Report Forms (CRFs) are being completed by authorised personnel as designated by the delegation log
- No key data is missing
- Data appears to be valid (i.e. within range and consistent)
- Check adherence to protocol and GCP
- Verify selected items recorded on CRFs match data in participants’ health records
- Confirm that the participant has provided written consent

Full details of the monitor’s responsibilities as noted in section 5.18.4 of ICH GCP can be found in Appendix 2.

3.5 Monitoring report
Following the monitoring visit, the monitors should provide to the CI and the JRCO copies of all monitoring reports which should include:
- Date, site, name of monitor
- Name of CI/Principal Investigator or other site personnel in attendance
- Summary of documents the monitor has reviewed, along with significant findings, deviations (if applicable), deficiencies, actions taken or recommended.

3.6 Trial Oversight committees
The funding body or sponsor may specify particular oversight arrangements. But even if they do not, some form of oversight is strongly recommended for all trials, although the appropriate structures will vary according to the size, complexity and risks associated with the trial.

Commonly employed oversight committees for a phase III trial include:

3.6.1 Trial Management Group (TMG)
Most trials should have a TMG, although in simpler trials this may comprise only one individual: the CI. For larger studies, this normally includes individuals who are responsible for the day-to-day management of the trial (e.g. the CI, trial coordinator, statistician, research nurse, data manager). The group’s role is to monitor all aspects of the conduct and progress of the trial, ensure that the protocol is adhered to and take appropriate action to safeguard participants and the quality of the trial itself.

3.6.2 Data Monitoring Committee (DMC)
A DMC should be considered for all trials, although one may not be always necessary (e.g. non first in man phase I/II studies). DMCs should be set up for all phase III clinical trials. Its role is to review the accruing trial data and to assess whether there are any safety issues that should be brought to the attention of the TSC or any ethical reasons why the trial should not continue.
The sponsor may consider establishing an independent data-monitoring-committee (IDMC) to assess the progress of a clinical trial, including the safety data and the critical efficacy endpoints at intervals and to recommend to the sponsor whether to continue, modify, or stop a trial (ICH GCP 5.5.2) also to assess whether there are any safety issues that should be brought to participants’ attention.

The DMC should be the only body that has access to unblinded data.

DMCs might consider using the DAMOCLES Charter proposed in the Lancet 2005 as a model for the organisation of the IDMC.

3.6.3 Trial Steering Committee (TSC)

The role of a TSC is to provide overall supervision of the trial and ensure that it is being conducted in accordance with the principles of GCP and the relevant regulations. It should agree the trial’s protocol and any protocol amendments and provide advice to the investigators on all aspects of the trial.

The TSC will usually have members who are independent of the investigators, e.g. an independent chairperson. All documentation produced by the TSC will include key decisions made during the trial and should be archived in the Trial Master File (TMF).

4. REFERENCES

JRCO/SOP/018: Trial auditing

JRCO/SOP/024: Maintaining training records


ICH GCP (1996), Section 1.8, 5.18 and 5.5.2

Imperial College Academic Health Science Centre, Joint Research Compliance Office, Monitoring Working Practice Document (WPD) JRCO/WPD/005, version 2, Effective Date: 03/04/12
APPENDICES

Appendix 1: Monitoring Assessment tool

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<th>Impact</th>
<th>Likelihood</th>
<th>Risk Score</th>
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<tr>
<td>Data management systems</td>
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<td>0</td>
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<tr>
<td>Mean Average</td>
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**Impact**

1. Low
2. Moderate
3. Significant
4. Major
5. Catastrophic

**Likelihood**

1. Remote
2. Unlikely
3. Possible
4. Likely
5. Certain

Impact x Likelihood = Risk Score.
Risk Score ÷ Number of hazards = Mean Average.

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<tr>
<td>High risk (ie 17-25)</td>
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CI Signature | Name (Print) | Date
-------------|--------------|---------
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<td>• Placebo?</td>
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<td>• TSC?</td>
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Appendix 2: Monitor’s responsibilities under ICH GCP (full details)

The monitor(s) in accordance with the Sponsor’s requirements should ensure that the trial is conducted and documented properly by carrying out the following activities when relevant and necessary to the trial and the trial site:

a. Acting as the main line of communication between the Sponsor and the investigator.

b. Verifying that the investigator has adequate qualifications and resources and remain adequate throughout the trial period, facilities, including laboratories, equipment, and staff, are adequate to safely and properly conduct the trial and remain adequate throughout the trial period.

c. Verifying, for the investigational product(s):
   (i) That storage times and conditions are acceptable, and that supplies are sufficient throughout the trial.
   (ii) That the investigational product(s) are supplied only to subjects who are eligible to receive it and at the protocol specified dose(s).
   (iii) That subjects are provided with necessary instruction on properly using, handling, storing, and returning the investigational product(s).
   (iv) That the receipt, use, and return of the investigational product(s) at the trial sites are controlled and documented adequately.
   (v) That the disposition of unused investigational product(s) at the trial sites complies with applicable regulatory requirement(s) and is in accordance with the sponsor.

d. Verifying that the investigator follows the approved protocol and all approved amendment(s), if any.

e. Verifying that written informed consent was obtained before each subject's participation in the trial.

f. Ensuring that the investigator receives the current Investigator's Brochure, all documents, and all trial supplies needed to conduct the trial properly and to comply with the applicable regulatory requirement(s).

h. Verifying that the investigator and the investigator's trial staff are performing the specified trial functions, in accordance with the protocol and any other written agreement between the sponsor and the investigator/institution, and have not delegated these functions to unauthorized individuals.

i. Verifying that the investigator is enrolling only eligible subjects.

j. Reporting the subject recruitment rate.

k. Verifying that source documents and other trial records are accurate, complete, kept up-to-date and maintained.

l. Verifying that the investigator provides all the required reports, notifications, applications, and submissions, and that these documents are accurate, complete, timely, legible, dated, and identify the trial.

m. Checking the accuracy and completeness of the CRF entries, source documents and other trial-related records against each other. The monitor specifically should verify that:
   (i) The data required by the protocol are reported accurately on the CRFs and are consistent with the source documents.
   (ii) Any dose and/or therapy modifications are well documented for each of the trial subjects.
(iii) Adverse events, concomitant medications and inter-current illnesses are reported in accordance with the protocol on the CRFs.
(iv) Visits that the subjects fail to make, tests that are not conducted, and examinations that are not performed are clearly reported as such on the CRFs.
(v) All withdrawals and dropouts of enrolled subjects from the trial are reported and explained on the CRFs.

n. Informing the investigator of any CRF entry error, omission, or illegibility. The monitor should ensure that appropriate corrections, additions, or deletions are made, dated, explained (if necessary), and initialled by the investigator or by a member of the investigator’s trial staff who is authorized to initial CRF changes for the investigator. This authorization should be documented.

o. Determining whether all adverse events (AEs) are appropriately reported within the time periods required by GCP, the protocol, the IRB/IEC, the sponsor, and the applicable regulatory requirement(s).

p. Determining whether the investigator is maintaining the essential documents.

q. Communicating deviations from the protocol, SOPs, GCP, and the applicable regulatory requirements to the investigator and taking appropriate action designed to prevent recurrence of the detected deviations.