Monitoring Clinical Trials

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Version 1.0	31 May 2007	1st Edition
Version 2.0	19 Jun 2008	Annual review
Version 3.0	08 Feb 2010	Formation of Joint Research Office
Version 4.0	14 Jul 2011	Annual review
Version 5.0	30 Nov 2012	Annual Review
Version 6.0	18 Feb 2015	Scheduled Review
Version 7.0	25 Oct 2017	Scheduled Review
Version 8.0	19 Oct 2020	Scheduled Review Templates removed and administrative changes to SOP. JRCO name change to RGIT
Version 9.0	02 Dec 2021	Review of non-ICHT monitoring oversight
Version 10.0	14 Mar 2024	Scheduled Review

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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 RGIT_SOP_018.

Monitoring of Clinical Trials of Investigational Medicinal Products (CTIMPs) is usually performed by the Research Governance and Integrity Team (RGIT) 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), RGIT monitors, and the CI or PI in monitoring Imperial College AHSC sponsored CTIMP studies will depend on whether the study is taking place in AHSC hospitals, College associated NHS Trusts or outside both AHSC sites and College associated NHS Trusts.

The Imperial College 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.
- Chelsea and Westminster Hospital NHS Foundation Trust and
- North West London Hospitals 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 RGIT, Imperial College AHSC. External Monitors are contracted to carry out the clinical research monitoring of external sites not listed above in accordance with the principles of GCP [see monitoring definition above].

3. RESPONSIBILITIES

All Clinical Trials of Investigational Medicinal Products (CTIMPs) Sponsored by the AHSC taking place at the AHSC sites or College associated NHS Trusts will be monitored as described in this SOP. Monitoring will be conducted by the RGIT Clinical Trials Monitor and overseen by the RGIT Clinical Trials Manager or delegate.

For AHSC sponsored CTIMPs which do not take place in any AHSC sites and/or College Associated NHS trust, the Chief Investigator (CI) or Principle Investigator (PI) has the responsibility to make appropriate monitoring arrangements. This equally applies to all studies in the AHSC sites and the College associated NHS Trusts with Contracted External Monitors. The RGIT monitor must inform the CI of the RGIT monitoring requirements during a meeting or via email. The RGIT requirements include providing the monitor with the following information:

- Contact details of the external Monitor(s) at the site(s).
- Copy of the Monitor(s) contract for the study (if applicable) or job description.
- Copy of the Monitor(s) signed and dated CV & GCP Certificates.
- External/local Monitor monitoring plan. This should be completed as per the RGIT template unless approved by the Clinical Trials Manager.
- Detailed reports of all monitoring conducted.

AHSC sponsored CTIMPs conducted through the Imperial College Trials Unit (ICTU) will follow their monitoring and SOPs. ICTU will be responsible for assessing the suitability of trial monitors, conducting their monitoring risk assessment and compiling the monitoring plan. ICTU will provide RGIT monitors with a copy of the monitoring plan prior to the commencement of the trial. ICTU Monitors will also provide the RGIT with copies of monitoring reports as stipulated in the RGIT-ICTU Delegation of responsibilities.

The RGIT monitor will review all monitoring reports from external/ICTU Monitors to uphold Sponsor requirements and will advise if there are any queries. This may be on a periodic basis as agreed with the vendor. The CI or PI must ensure that all the above requirements are met.

RGIT Oversight for sites external to AHSC sites and/or College Associated NHS:

- RGIT monitor to be in receipt of the following documents prior to issuing green light for ICHT Sites or ICHT study external sites:
  - Completed SIV Monitoring Report
  - Copy of SIV slides
  - Study Start Approval form (SSA Form)
  - RGIT Monitors checklist
  - Monitoring Risk Assessment & Monitoring Plan
  - Capacity and Capability Approval
  - Signed site contract
  - A copy of the CI or Site PI's current CV & GCP Documents
- ICTU Managed CTIMPs: ICTU to issue green light & forward greenlight confirmation to RGIT (No RGIT involvement required).

RGIT monitor to track each site in the study and to record RGIT, ICTU or other delegate green light for each site as well as periodic contact with external monitor on study site status and monitoring that has been conducted.

All external monitoring to comply with RGIT monitoring templates and requirements unless agreed differently by the RGIT Clinical Trials Manager or delegate.

4. PROCEDURE

4.1. 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 RGIT_SOP_024.

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

4.2. Types of monitoring

4.2.1 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 is missing
- Data appears to be valid (e.g., within range and is consistent)
- A review of recruitment rates, withdrawals and losses to follow-up

4.2.2 Central (Remote/Off site) 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, skewedness). 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 is "too good" should raise suspicion in the same way as data that is unusually poor.

4.2.3 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 & consistency and confirm all assessments are made by appropriately qualified staff.
- To identify staff training needs.

4.2.3.1 On-site Visits

a) <u>Site Initiation Visit</u>

The RGIT Trial Monitor will perform the SIV at all Imperial College London/Imperial College Healthcare NHS Trust research sites. The SIV for all other research sites must be conducted by an external monitor or appropriate member of the lead research team. An SIV cannot be performed until there is assurance that site agreement(s), all other relevant regulatory approvals are in place

The SIV will be arranged so that the CI/PI and other key members of the study team can attend (e.g., Study doctor, research nurse, Lead pharmacist, etc). a list of attendees will be collected.

A presentation will be given to the site to detail the responsibilities of the research team, as required by the sponsor. This will include at least the following:

- GCP and staff training
- The Informed Consent Process

- Safety Reporting
- Investigational Medicinal Product
- Protocol Deviations and Violations
- Trial Documentation
- Data Entry
- Laboratory
- Equipment calibration certificate or SOP to demonstrate calibration is done
- Annual Reports
- Amendments
- End of Study
- Trial-specific procedures

The RGIT Monitor will check that all the documents required for the study to start the research are present. If the monitor is satisfied that all documents are present, the CI can sign the Study Start Approval form (SSA form), previously signed by the RGIT Clinical Trials Manager. Otherwise, the SSA will be withheld pending a successful SIV.

b) Routine Monitoring Visit

The monitor will perform the following activities during each site monitoring visit:

- Review all subject informed consent forms
- Complete SDV as per requirements of the monitoring plan
- Review data quality
- Review the Trial Master File/Investigator Site File:
  - Review essential documents
  - Ensure the SAE log is complete and filed
  - Ensure that all Ethics reporting requirements have been met
  - Ensure trial logs have been updated
- Discussion with the site staff and principle investigator on new issues and unresolved issues from monitoring visit, patient recruitment, site's compliance to protocol
- Review pharmacy file and IMP Accountability Logs along with temperature logs
- Review Delegation of Duties and Site Signature Log

After the monitoring visit the RGIT Monitor will write the monitoring report including a list of all missing documents and issues raised that need to be resolved. This should be completed and sent to the site within 2 weeks and a response received from the site no later than 30 days after they have received the report.

c) Site Close Out Visit (COV)

A COV will be performed after the trial has been completed (or if the study has terminated early). The Trial Monitor will arrange the visit at a convenient date and time with the site staff and notify them in writing. At sites which are not part of the Imperial College Healthcare Trust, the delegated monitor will need to perform the close out visits.

The COV will comprise of a full site file review and source data verification. It will also include ensuring that all listed actions from previous monitoring visits are resolved. The monitor will ensure data entry is complete and that all outstanding queries are resolved.

The pharmacy file will also be closed, and a final accountability of IMP stock and returns will be conducted. Destruction of any remaining IMP will need to be approved by the CI/PI.

The trial monitor will discuss archiving requirements with the study team and provide assistance where required. Results reporting and upload to EudraCT will also be reviewed with the study team.

After the Close Out monitoring visit the RGIT Monitor will write the monitoring report including a list of all missing documents and issues raised that need to be resolved.

4.3. Extent of monitoring

The sponsor should ensure that the trials are adequately monitored. To determine the appropriate extent and nature of monitoring, a Monitoring Risk Assessment should be completed for each trial. This risk assessment should be based on the objective, purpose, design, size, complexity, blinding, endpoints and risks associated with the clinical trial. If a CTIMP study is assessed as "high risk" or is First in Mankind, it will automatically be considered as "high risk". Once a Risk Assessment has been completed, the RGIT monitor will then agree the frequency of routine monitoring visits with the CI of the study and Clinical Trials Manager.

4.3.1 Risk Assessment

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

Based on the Risk Assessment, a Monitoring Plan will be put in place by the RGIT Team describing all monitoring activity for the Clinical Trial. The Monitoring Plan needs to be agreed with the CI. In general, for most studies there will be a need for on-site monitoring, however, in some academic clinical trials and extenuating circumstances, the CI in conjunction with the RGIT, may decide that remote monitoring and self-assessed monitoring alongside relevant training and meetings with extensive written guidance can assure appropriate conduct of the trial. The RGIT 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.

4.4. 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.

4.5. Monitoring report

Following the monitoring visit, the monitors should provide to the CI, pharmacy and the RGIT copies of all monitoring reports which should include:

- Date of visit, site name and name of monitor
- Name of CI/Principal Investigator or other site personnel in attendance
- A Summary of the documents the monitor has reviewed, along with significant findings, deviations (if applicable), deficiencies, actions taken or recommended.

When a protocol violation is identified, the sponsor will advise on what action is required and may initiate a triggered audit. For IMP trials requiring MHRA approval, should the violation be identified as a serious breach, the Sponsor will inform the MHRA of the incident within seven days.

4.6. 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:

4.6.1 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.

4.6.2 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.

4.6.3 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).

Trial teams must send meeting minutes from the TMG, TSC and DMC meetings to the RGIT for our records via the following email: rgit.ctimp.team@imperial.ac.uk.

5. REFERENCES

RGIT_SOP_018: Audit (SOP, Associated Documents & Templates page (Last Cited: 10 Mar 2023))

RGIT_SOP_024: Training (SOP, Associated Documents & Templates page (Last Cited: 10 Mar 2023))

CT-Toolkit: Trial Management & Monitoring (Last Cited: 13 Mar 2023)

DAMOCLES Study Group (2005) A proposed charter for clinical trial data monitoring committees: helping them to do their job well. Lancet 365: 711-722

ICH: E 6 (R2): Guideline for good clinical practice - Step 5 (europa.eu) Sections 1.8, 5.18 and 5.5.2 (Last Cited: 10 Mar 2023).

NHS R&D Forum. *Distinguishing different types of Monitoring and Audit*, November 2008
JRO UK regulations Compliance form (Part 2), version 1.0

6. APPENDICES

The following Appendices list the following Templates associated to this SOP which can be found on the SOP, Associated Documents & Templates page.

Appendix 1: Monitoring Risk Assessment – RGIT_TEMP_029
Appendix 2: Monitor's responsibilities under ICH GCP – RGIT_TEMP_030