UTS IMPACCT Trials Coordination Centre

Standard Operating Procedure

5.18 Monitoring

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Introduction / Background

The purpose of monitoring is to undertake a detailed review of the study documentation, protocol implementation and procedures, to correct outstanding data queries, and to assess and provide support for site specific problems.

The IMPACCT Trials Coordination Centre (ITCC) undertakes monitoring of PaCCSC/CST studies to ensure the investigating sites comply with Good Clinical Practice (GCP), the applicable regulatory requirements, the protocol, and the Standard Operating Procedures relevant to the study.

ITCC monitoring activities follow a risk-based approach involving a combination of ongoing centralised monitoring of trial activities throughout the trial as well as on-site and telephone (remote) monitoring visits. The frequency of monitoring visits is determined by a risk assessment of each site and the application of monitoring triggers as defined in the Protocol and/or Study Monitoring Plan.

The ITCC monitor examines relevant study documents, Case Report Forms (CRFs), reports, correspondence, etc. Issues identified during monitoring visits and correction plans are discussed with the site team along with a written report following the visit.

Pharmacy monitoring is undertaken by a trained and unblinded ITCC monitor or through an independent sub-contractor with expertise in the area. Pharmacy monitoring is unblinded and includes a review of the pharmacy folder, compliance with randomisation schedules, study medication accountability, storage and destruction of study medications.

At on-site visits, the study monitor is given access to all study related material, and adequate space and privacy in order to review the materials, including access to source documents as required.

Central monitoring activities undertaken by the ITCC involve the development and maintenance of two separate REDCap projects for each trial:

1. Forms and Documents (Template 47) project: A repository of essential documents including ethics and regulatory documents, HREC approved study documents such as protocol, consent forms, questionnaires and other assessment tools, recruitment and retention materials as well as data collection worksheets, guides and instructions, master documents for the Investigator Site File (ISF) and site initiation training materials. This database ensures that all sites have access to the same documents. Each site is expected to refer to this repository to access the approved forms and documents for each study and to update the local ISF.

2. Tracking project: This project functions as a Clinical Trial Management tool to internally monitor all aspects of the trial at site level including ethics (central and local) and regulatory approvals, site initiation training and site activation, recruitment, site monitoring including issues and protocol violations as well as invoicing and payments.

The ITCC utilises these two projects, in parallel with continuous review of the data entered in the electronic CRF database to centrally monitor randomisation, safety reporting, data quality, and recruitment at both the overall trial and individual site level for all PaCCSC/CST studies. The ITCC also monitors internal activities such as compliance with ITCC SOPs, timeframe to process agreements, contracts and invoices, study site staff changes as well as compliance requests with the Data Safety Monitoring Committee, relevant Scientific Advisory Committee, or other relevant committee(s) to ensure continuous organisational and operational performance.

Objective

This SOP:

- Defines the role and responsibility of ITCC monitoring;
- Describes the monitoring process;
- Describes the process of reporting results and action that arises from those results;
- Ensures there is capacity building across the network through ongoing training during monitoring.

Scope

This SOP applies to all staff involved in clinical studies conducted by ITCC/PaCCSC/CST irrespective of individual organisational employment, role or position.

Ownership and Responsibility

Monitoring of PaCCSC/CST clinical studies is the responsibility of the ITCC. All monitoring visits are conducted in the presence of the Principal Investigator and/or other designee(s) as documented in the Staff Signatures and Delegation Log (*refer* SOP 4.2.4 Delegation of Duties).

Procedure

1. Timeframe

- Monitoring is undertaken as per the Study Monitoring Plan (Template 35) or as specified within the study protocol.
- For Phase III studies, monitoring is conducted during the entire recruitment period and prior to study conclusion. Additional monitoring (on-site or remote) is conducted at the request of other relevant committees.

2. Central Monitoring

- Once a study is endorsed by the relevant Scientific Advisory Committee and receives funding to commence, the ITCC initiates the development and maintenance of the 'Forms and Documents' and 'Tracking' projects specific for the study. It is the responsibility of the ITCC to update both of these projects throughout the lifecycle of the study.

3. Monitoring sites

- Each individual study site for a specific study is monitored. For Phase III PaCCSC/CST/ITCC studies, the study sites are the participating sites.

4. Personnel involved

- Ideally, all monitoring visits are completed by an appropriately trained and experienced staff member of the ITCC. The ITCC monitor may work with a support monitor (co-monitor).
- All monitoring visits are conducted in the presence of the Principal Investigator (or delegate) of the site being monitored.

5. Extent

Each monitoring visit, whether on-site or remote is designed to ensure that:

- The study is conducted in accordance with the protocol and appropriate regulatory requirements;
- Consent has been obtained for every participant;
- Deviations from the protocol are documented and reported (Template 8);
- Data on Case Report Forms can be verified;
- Patients enrolled meet the eligibility criteria;
- All safety assessments are reported appropriately and any serious adverse events are followed up until resolution;
- Personnel at each site are meeting GCP obligations;
- Randomisation, allocation and study medication accountability procedures are being followed.

The monitor is able to discuss recruitment and retention issues, clarify protocol issues, and provide training and support, such as worksheets and tracking documents.

6. Preparation for a monitoring visit

The ITCC formally notifies the site of the upcoming visit date, after negotiating the most suitable date within the required visit timeframe specified in the Study Monitoring Plan.

The Principal Investigator (or delegate) ensures the site is adequately prepared for a visit (*refer* Guidance 4) providing the following:

For On-Site Monitoring Visit:

- A quiet space;
- An up to date Investigator Site Folder (ISF);
- Provides all completed data collection worksheets for the participants to be monitored;
- Organises access to other relevant source data (especially electronic medical records, etc.), if applicable;
- Schedules time to be available to discuss study progress with the monitor during the visit.

For Telephone (Remote) Monitoring Visit:

- Ensures that all completed data collection worksheets for the participants to be monitored are uploaded to the eCRF database prior to the visit;
- Ensures all eCRF data entry is complete for the participants to be monitored;
- Provides a copy of the most current and up to date Staff Signature and Delegation Log, Training Log and Monitoring Visit Log.

7. Visit procedure

All critical data elements undergo 100% validation checking at each monitoring visit. Critical data elements are:

- Subject existence
- Eligibility
- Informed consent
- Primary end points
- Safety
- Administration of study medication
- Study termination (treatment cessation or withdrawal)

During telephone (remote) monitoring, physical review of the participant files and medical records is not possible but the focus of the monitoring activities is to review the data collection worksheets and eCRF and to obtain verbal confirmation from the site staff that the above critical data elements are documented in the participant's medical records/clinical notes.

In addition, other items may also be reviewed as needed during telephone visits to assess overall site health and compliance:

- Protocol deviations and violations
- Recruitment activities, eCRF data entry and completion of participant data collection worksheets
- Discussion of issues identified during data verification activities
- Site staff changes and resources at the site
- Assessment of requirement for additional site staff training
- Unresolved corrective action items or site issues

- Recurring issues such as those related to consent, documentation, delegation of duties, and issues related to organisation, access to information or source data
- Availability of important regulatory and essential documents in the ISF such as CVs, training records, HREC/RGO documentation, Serious Adverse Event Reports etc.

Each of the critical components are coded according to the level of deficiency following the on-site or remote review:

- None
- Minor
- Major

During the monitoring process (Guidance 5), the monitor documents issues and deficiencies on a Corrective Actions Sheet (Template 15). The Corrective Actions Sheet is used to summarise all findings identified during the monitoring visit including any protocol deviations or violations. The monitor is responsible for entering possible solutions for all findings.

Protocol violations identified during monitoring activities are logged into the Protocol Deviation/Violation Log and reported to the lead Investigator using a Protocol Violation Form (Template 8) (*Refer* to SOP 4.5 Protocol Deviations and Violations).

At the conclusion of an on-site monitoring visit an exit meeting is held with the Principal Investigator (if available) and study team members to discuss the main summary findings of the visit and the likely content of the report. The required outcome for all findings documented on the Corrective Actions Sheet is completed with the site staff during the exit meeting. At telephone (remote) monitoring visits, the findings and required outcomes are discussed with site staff throughout the call as they are identified.

When possible, a copy of the Corrective Actions Sheet is made during an on-site visit following the exit meeting. The original is left with the site and the copy is taken by the monitor and sent to the ITCC for filing. If this is not possible due to time constraints or following a telephone (remote) visit, a copy of the Corrective Actions Sheet is emailed to the site staff along with the monitoring report.

At the conclusion of each on-site or remote monitoring visit, the monitor(s) signs the Monitoring Log (Template 16) as a record of the visit.

8. Monitoring report

Within 14 calendar days following the monitoring visit, the Principal Investigator and site staff are emailed a copy of the Corrective Actions Sheet and a summary of the following information:

- Date(s) of monitoring visit
- Name of site and site personnel in attendance
- Name of monitor(s)
- A summary of the review process
- A summary of the findings, for the site and the organisation (contains a description of all major deficiencies in the 2 locations and the 7 critical components reviewed)

The site being monitored is assigned an assessment of:

- Acceptable

- Acceptable needs follow-up
- Unacceptable
- Conclusions and recommendations (a general assessment of the review)
- Follow-up required

This summary email and the accompanying Corrective Actions Sheet constitutes the site visit monitoring report. Both of these documents must be filed in the ISF.

The Principal Investigator is also required to confirm by reply email to acknowledge receipt and review of the monitoring report email and the findings summarised therein.

In the event that recurring notable issues or serious breaches are identified at a monitoring visit, a follow-up telephone call will be scheduled with the Principal Investigator to discuss an appropriate corrective and preventative action plan.

9. Monitoring visit follow-up

The Monitoring report/email may require a response by the study site to specific issues raised during the monitoring visit. This response is provided, in writing, within 30 calendar days of receipt.

a. Monitor discusses deficiency with the Principal Investigator (or delegate) and agrees on appropriate action.
b. If the monitor is not satisfied with the response from the Principal Investigator, the matter is discussed with the Coordinating Principal Investigator of the relevant study to determine what further action is required.
c. Any ongoing concerns are referred to the relevant Scientific Advisory Committee for discussion and resolution.
d. Any on-site or remote monitoring visit with a final assessment of ‘Unacceptable’ will be referred to the Coordinating Principal Investigator who will convene an out of session meeting of the relevant committee (Scientific Advisory Committee or Data Safety Monitoring Committee) so a decision can be made regarding ongoing recruitment at that site.

The site is responsible for ensuring the Corrective Actions Sheet is completed and returned to the monitor for checking, along with any evidence to support compliance with the findings of the visit (*refer* Guidance 4).

10. Study monitoring report

The study monitor provides a study wide report on conclusion of the study in accordance with the study specific monitoring plan.

Related SOPs

4.2.4 Delegation of Duties
4.5 Protocol Deviations and Violations
5.19 Auditing
8.0 Essential Documents

Related documents

Template 8: Protocol Violation Form
Template 15: Corrective Actions Sheet
Template 16: Monitoring Log
Template 35: Study Monitoring Plan
Template 47: Forms and Documents
Guidance 4: Monitoring Guidelines for Sites
Guidance 5: Monitoring Guidelines for Monitors

References

National Statement on Ethical Conduct in Human Research (2007) - Updated 2018- (accessed 31/03/2020) https://www.nhmrc.gov.au/about-us/publications/national-statement-ethical-conduct-human-research-2007-updated-2018

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International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH). Integrated Addendum to ICH E6(R1): Guideline for Good Clinical Practice E6(R2). November 2016 (accessed 14/02/2022)

https://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E6/E6_R2__Step_4.pdf

International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH). General Considerations for Clinical Studies E8(R1). October 2021 (accessed 14/02/2022)

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Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95). Annotated with TGA comments 2000 (accessed 31/03/2020)

https://www.tga.gov.au/sites/default/files/ich13595an.pdf

Australian Code for the Responsible Conduct of Research 2018 (accessed 31/03/2020) https://www.nhmrc.gov.au/about-us/publications/australian-code-responsible-conduct-research-2018

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History			
Version	Date	Author	Reason
1.1	18/07/2007	B Fazekas	New procedure
1.2	13/08/2007	B Fazekas	Ratified by MAB
1.3	16/10/2007	B Fazekas	Update following review by David Currow
1.4	30/12/2009	B Fazekas	Update following monitor training
1.5	2/09/2010	B Fazekas, Tania Shelby-James	Periodic review
2.0	3/02/2011	B Fazekas	Changes ratified by MAB
2.1	20/05/2015	C Hope	Periodic review
2.2	28/02/2018	B Fazekas, S Kochovska	Periodic review Publication of the ICH GCP E6 (R2)
2.3	06/12/2018	L Brown	Update to include CST and ©
2.4	31/03/2020	C Strauss	Periodic review Update to include risk-based monitoring activities and implementation of telephone (remote) visits Publication of Australian Code for Responsible Conduct of Research (2018) and National Statement on Ethical Conduct in Human Research (2007) Updated 2018. Updated to include IMPACCT Trials Coordination Centre
2.5	14/02/2022	C Strauss	Periodic review Update to risk-based and central monitoring activities and procedures Publication of ICH GCP E8(R1) guidelines

Approval		
Version	Approval Name	Approval Signature
2.5	Meera Agar