MELBOURNE HEALTH	OFFICE FOR RESEARCH (OFR) STANDARD OPERATING PROCEDURE (SOP) CLINICAL TRIAL MONITORING PLANS and MONITORING VISIT ACTIVITIES		
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1. AIM

To describe the process of monitoring a research trial and implementation of a trial monitoring plan for clinical trials, including trials conducted under the Clinical Trial Notification (CTN) scheme, instigated and/or sponsored by Melbourne Health (MH) employees and conducted under the auspices of MH as singe or multi-site trials.

2. SCOPE

Monitoring of a trial is required for all phases of MH investigator initiated single site and multi-site clinical trials of medicinal products, devices and diagnostics when MH has initiated the research and/or is the trial CTN sponsor.

Note: for monitoring activates for non-clinical trial/general research studies refer to the SOP 'Research Study Monitoring and Monitoring Plans (non-clinical trials).

3. APPLICABILITY

Sponsor

MH is the sponsor for investigator initiated clinical trials where MH has written the protocol and/or is named on the CTN.

MH delegates sponsor activities including the development and implementation of the trial monitoring plan, management and documentation of trial monitoring to the MH study Principal Investigator (PI) for single site studies or MH Coordinating Principal Investigator (CPI) for multi-site studies.

Coordinating Principal Investigator (CPI)/ Principal Investigator (PI) and Study Team

The CPI is responsible for the overseeing the conduct of the entire trial at each site of a multi-site trial including ensuring that appropriate monitoring of studies in accordance with this procedure and any other applicable requirement.

The PI is responsible for the conduct of the entire trial at the site including ensuring that appropriate monitoring of site studies in accordance with this procedure and any other applicable requirement.

Other trial personnel are responsible for conducting monitoring activities under the direction of the PI in accordance with the delegation log and this procedure.

Monitor(s)

The study monitor(s) is responsible for conducting trial monitoring activities as delegated by the PI in accordance with the delegation log and this procedure. The study monitor should follow the trial monitoring plan and comply with all applicable MH policy and guidelines, legislation and guidelines.

4 PROCEDURE

4.1 Introduction

Monitoring of research is a quality measure and is a requirement of the National Statement on the Ethical Conduct of Human Research, 2018 (National Statement), and the Good Clinical Practice (GCP) guideline.

ICH GCP defines monitoring 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, Standard Operating Procedures (SOPs), GCP, and the applicable regulatory requirement(s).

The purpose of trial monitoring is to verify that:

(a) The rights and well-being of participants are protected.

(b) The reported trial data are accurate, complete, and verifiable from source documents.

(c) The conduct of the trial complies with the currently approved protocol, approved amendment(s), GCP guidelines, and applicable regulatory requirement(s).

The monitoring plan describes in detail the extent of the monitoring of a clinical trial and should:

- Be completed as an element of protocol development and study feasibility / management planning.
- Be tailored to the specific human participant protection and data integrity risks of the trial.
- Describe the strategy, methods, responsibilities, and requirements for monitoring the trial.
- Be included in the applications for ethical and research governance (site specific assessment) review.

All research studies including clinical trials must comply with applicable legislation, policies and guidelines including:

- Australian Code for the Responsible Conduct of Research (2018)
- The National Statement on Ethical Conduct in Human Research, 2007 (updated 2018)
- Therapeutic Goods Act (1989)
- Melbourne Health Research Policy MH18
- Melbourne Health Research Integrity Guideline
- Integrated Addendum to ICH E6 (R1) Guideline for Good Clinical Practice E6 (R2)

4.2 MH as sponsor

Where MH is to act as a clinical trial sponsor, Principal Investigators (PI) will need to provide evidence that adequate management and processes are in place to support MH in meeting its sponsor requirements for the conduct of the trial, including in respect to trial monitoring.

Applications to request MH to act as the CTN/TCX sponsor for clinical trials of unapproved therapeutic goods (drugs, devices or biologicals) must be made to The Office for Research prior to submission of studies for ethical review.

Refer to the OFR webpage "Submit a research governance (site-specific) application" at https://www.thermh.org.au/research for further information on the process to request MH act as sponsor for a MH investigator initiated for a CTN/TCX clinical trial.

4.3 Budgeting for monitoring activities

Investigators are strongly encouraged to:

1. Include monitoring costs in the trial budget.

2. Include monitoring costs in funding applications (i.e. grant applications, funding from companies etc.).

3. Cconsider using monitors from a Clinical Research Organisation (CRO) but this may not always be feasible and other options may be investigated, including using internal staff and directly contracting with experienced monitors.

4.4 Monitoring of single site MH initiated clinical trials

The MH PI is responsible for development and implementation of the trial monitoring plan for single-site MH initiated clinical trials.

Monitoring may be performed by MH staff or external contracted persons or entities acting under the supervision of the MH PI.

4.5 Monitoring of multi-site MH initiated clinical trials

Where MH is the sponsor, the MH PI must also act as the study Co-ordinating Principal Investigator (CPI).

Whether MH acts as CTN sponsor for non-MH sites will be determined by the MH Office for Research on a case by case basis.

Each participating site must each enter into an agreement with the lead site.

The agreement should include the specific timing and duties concerned with monitoring and quality assurance, which are delegated to the sites according to the monitoring plan.

The agreement should be executed prior to inclusion of trial participants at the site.

4.6 Monitors

The CPI/PI is responsible for:

- Appointing and managing the study monitor(s).
- Ensuring that the study monitor(s) are appropriately trained and experienced to undertake the role of study monitor.

The study monitor(s) may be identified internally (from the study team or other MH employees) or externally to MH (i.e. contracted to MH for the purpose of monitoring, via engagement of a Contract Research Organisation (CRO)). Where an external monitor is used, they may be contracted to carry out all or a proportion of monitoring activities.

The study monitor is responsible for acting under the direction of the CPI/PI.

In the case of external monitors, study monitor is responsible for acting:

- Under the direction of the CPI/PI the CPI/PI if contracted directly to MH; or
- Under the direction of the CRO where a CRO is contracted to undertake monitoring activities.

Monitors should act with professionalism, honesty, integrity and maintain privacy at all times.

Monitors must sign a confidentiality agreement with their employer (MH or a CRO). If a CRO is engaged to monitor a study, the MH-CRO agreement must include a section outlining how confidentiality will be maintained by CRO employees involved in activities covered by the agreement at MH and with MH information.

The study monitor(s) responsibilities include:

- Verifying adherence to GCP guidelines.
- Monitoring adherence to the HREC-approved protocol and reporting serious breaches to the CPI/PI.
- Performing site initiation visits.
- Assisting sites with logistical issues as needed.
- Performing routine monitoring visits.
- Assisting the PI and study team in the preparation for any potential governance/regulatory audit(s).

4.7 Complete a Risk Assessment in Preparation for development of the Monitoring Plan

Traditionally commercially sponsored clinical trials have undergone 100% source data verification (SDV). However, more recently the industry has recognised that risk-based monitoring is a time and cost-effective way to monitor studies.

The National Statement on Ethical Conduct in Human Research (2007) (National Statement) permits monitoring arrangements to be commensurate to the risk, size and complexity of the trial.

A trial specific risk-based monitoring approach should increase the likelihood of the monitoring plan to identifying conformance to key requirements.

A risk assessment should be completed in preparation for completion of the trial monitoring plan.

The aim of risk assessment is to identify the potential risks and critical processes/data before initiation of a trial.

Note: where possible risks should be eliminated. Where risk cannot be eliminated, protocols and supporting procedures should include methods to identify and manage risks and where required report incidents.

When performing risk assessment, a combination of assessors should be involved where possible, including:

- Persons with knowledge in the respective medical indication and research field.
- Persons with knowledge regarding the clinical procedures at the sites.
- Pharmacist, radiologist, biochemist, statisticians and other specialists when relevant.

Risk evaluations must be related to protection of the rights, safety, and well-being of trial subjects and the credibility of the trial results.

The scope of risks considered for a trial should include but is not limited to:

- Protocol activities – complexity, time constraints, resource constraints etc.
- The risk of the trial intervention(s) relative to standard care and the extent of knowledge about the IMPs/IMDs being tested.
- Credibility of key data – i.e. data points are critical to the defined outcomes. How the data are generated, collected, registered, and reported in the risk assessment process.
- Number of sites involved in the trial.
- Established quality assurance systems like laboratory guidelines, temperature control of medication storage rooms, central monitoring etc.
- For participants - physical, emotionally, rights, privacy etc.
- For researcher's – experience, reputation, capacity to receive funding etc.
- For the institution - demand on/availability of resources, reputation, financial, capacity to receive funding etc.

The risk assessment should be reviewed periodically during conduct of clinical trials and when changes in risk are identified.

4.8 Complete the Monitoring Plan

Complete the trial monitoring plan template. Delete instructions and hints in the template before finalising the document.

The appropriate extent and nature of monitoring should be determined for a trial based on considerations such as;

- A risk assessment of the trial intervention(s) relative to standard care and the extent of knowledge about the investigational medicines and/or devices being tested.
- The complexity of the trial protocol and supporting processes. Is it a retrospective data analysis or clinical trial? Include factors such as objective, purpose, design, complexity, blinding, size, and endpoints of the trial.
- Experience of the research team.

Statistically controlled sampling may be an acceptable method for selecting the data to be verified.

The trial monitoring plan document should:

- Describe the monitoring strategy, responsibilities of all the parties involved, the various methods to be used, and the rationale for their use.
- Be developed a systematic, prioritized, risk-based approach and emphasize the monitoring of critical data and processes. Particular attention should be given to those aspects that are not routine clinical practice and that require additional training.
- Identify the visit schedule and describe the types of visits to be conducted i.e. interim monitoring visits, for-cause visits and close out visits.
- Where the scope of monitoring permits, use varied approaches that improve the effectiveness and efficiency of monitoring (i.e. on-site monitoring only, a combination of on-site and centralized monitoring, or, where justified, centralized monitoring only).
- Document the rationale for the chosen monitoring strategy in the monitoring plan.
- Reference the applicable policies and procedures.

The monitoring plan should be documented and continually reviewed and adapted during the trial, as real time assessments of safety data are performed (Safety monitoring and reporting in clinical trials involving therapeutic goods 2018).

4.9 Types of Study Visits

There are several types of study visits that may occur over the course of a study: site initiation visit (SIV), interim monitoring visits (on-site or remote), for cause visits and close out visits.

Note: refer to section 4.11 and the appendices of this document for list of activities that may be conducted at the visits.

- **Site initiation visits** – This is not usually classed as a monitoring visit. The purpose of the SIV is visit is to confirm that all elements required to conduct the project are in place and ready for the project to start and include: the issue of all project approvals, the site processes are appropriate study specific process have been established, delegations and training have been completed.

  For further information on site initiation visits refer to MH GCP SOP 008 Site Initiation and Close Out.

- **Interim monitoring visits** - are visits scheduled between the SIV and close out visit. Interim monitoring visits may be scheduled on-site visits or a combination of on-site visits and remote visits.

- **For-cause visits** – monitoring visits conducted in response to an event i.e. a safety event or serious.

- **Remote Monitoring** – also called centralised monitoring. Review of information that is routinely provided to /requested by the sponsor. Remote monitoring is generally conducted off-site (i.e. at the sponsors site).

  Where remote monitoring visits are scheduled in the monitoring plan, the sponsor should ensure:

  - that the site is aware of the extra procedures that may be involved for remote monitoring and may include Investigator/study team training, regular meetings, SOPs including for the forwarding documentation to the monitor and answering queries.

  - the study agreement includes clauses that adequately describe the provision of associated procedures.

  Note: while remote monitoring may reduce the need for onsite visits, it is recognised that remote monitoring does not entirely replace on-site monitoring completely. Most importantly information about the site function and processes as well as building a good rapport with site study team are critical outcomes of onsite monitoring. Further, remote monitoring of complex studies may not be possible for all elements of monitoring functions.

- **Close out visits** - are visits scheduled at the end of the study and must be completed before the study is closed. The purpose of the Close out visit is to ensure that all study activities and documentation have ben satisfactorily completed prior to closing the study.

4.10 Determine the schedule of interim monitoring visits

The frequency of interim monitoring visits is dependent on the risks associated with the trial. The risks may include trial phase, nature of the intervention, complexity of procedures, rate of participant recruitment.

Refer to the risk assessment when determining the schedule for interim monitoring visits.

The first interim monitoring visit should be scheduled as soon as possible after the first participant receives the intervention, and usually within 6-8 weeks of the intervention.

Each site should have an on-site monitoring visit at least once per year during the active phase of the study.

Monitoring should continue until the last participant has completed follow-up evaluations in accordance with the protocol.

For multisite visits, the monitoring schedule should be agreed to by the participating site and included in the trial agreement along with clauses describing the responsibilities of all parties and associated procedures.

Refer to the OFR Study Monitoring Plan for Clinical Trials for further information.

4.11 Monitoring Activities

During the monitoring visit, the Monitor should undertake activities outlined in the monitoring plan and in consideration of the trial recruitment status.

- **Access to study personnel**

  During a monitoring visit, the CPI/PI/ delegate should ensure access to all requested trial-related records.

  The CPI/PI should schedule time to be available for monitoring visits; at the start of the visit to answer questions, and at the close of the visit for a summary of findings.

  Other trial personnel, usually the Study Coordinator (SC) or delegate, should be available, as needed during the visit, meet with and to provide documentation and answer queries to the monitor.

- **On-site monitoring activities include:**

  The monitor(s) in accordance with the monitoring plan, should ensure that the trial is conducted and documented properly.

  Activities may include:

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

  (b) 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 participants who are eligible to receive it and at the protocol specified dose(s).

(iii) That participants 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.

(c) Ensuring that the investigator and the investigator's trial staff are adequately informed about the trial.

(d) Verifying that written informed consent was obtained before each participant's participation in the trial.

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

(f) 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.

(g) 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 is enrolling only eligible participants.

(i) Reporting the participant recruitment rate.

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

(k) 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.

(l) 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 participants.

(iii) Adverse events, concomitant medications and intercurrent illnesses are reported in accordance with the protocol on the CRFs.

(iv) Visits that the participants 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 participants from the trial are reported and explained on the CRFs.

(m) 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.

(n) Determining whether all adverse events (AEs) are appropriately reported within the time periods required by GCP, the protocol, the reviewing ethics committee, the sponsor (MH as sponsor/research governance organisation), and the applicable regulatory requirement(s).

(o) Determining whether the investigator is maintaining the essential documents.

(p) 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.

(q) Sign the monitoring log

4.12 Does the Clinical Monitoring Plan require ethics approval?

The monitoring plan does not require separate ethical approval. However, details of the monitoring plan should be included in the trial protocol or other study documents that are submitted to the reviewing ethics committee for review as part of planned study activities.

4.13 Reviewing the Trial Monitoring Plan

The study monitoring plan should be reviewed and updated:

- periodically to ensure that it still meets the needs of the study
- in response to changes in risks of the study including identification of new risks
- in response to outcomes of monitoring activities that identify deficiencies and where corrective/preventive action plans require more frequent monitoring.

Changes in the trial risk profile may arise from:

- Identification of risk that were not previously considered.
- Evolving protocol - amendment to the protocol that affect the risk profile of the trial.
- Change in technologies.

- Change in policies, legislation or other requirements.

The review of monitoring plans should be documented.

4.14 What to do with your completed trial monitoring plan

- Train staff who will implement the plan in the requirements of the plan.
- FOLLOW IT – implement the plan and schedule monitoring activities.
- Depending on the size of complexity of the trial monitoring plan, it may be included in the trial protocol or maintained as a separate document.
- The trial monitoring plan is an essential trial document and should be filed in the trial folder.
- All site-related materials should be made available for review, by auditors or regulatory authority(ies) and the sponsor's representatives (sponsored studies) for ALL studies.

5. Dissemination and Implementation

This SOP will be disseminated by the Office for Research. Updates will be made available with details of planned dates of implementation.

6. Monitoring Compliance and Effectiveness

Compliance with this SOP will be monitored as part of the Office for Research monitoring process. Any problems or potential problems concerning the effectiveness of this SOP may be identified during the Office for Research monitoring process or through users informing the Office for Research.

7. Review and Updating

This SOP will be reviewed every three years, or whenever there are changes to legislation or working practices that impact upon the content of this document. This SOP may be merged with another SOP if appropriate or removed entirely if it becomes redundant.

8. GLOSSARY

Essential Documents

Documents which individually and collectively permit evaluation of the conduct of a trial and the quality of the data produced

Good Clinical Practice (GCP)

A standard for the design, conduct, performance, monitoring, auditing, recording, analyses, and reporting of clinical trials that provides assurance that the data and reported results are credible and accurate, and that the rights, integrity, and confidentiality of trial participants are protected.

International Conference on Harmonisation (ICH)

International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use is a joint initiative involving both regulators and research-based industry focusing on the technical requirements for medicinal products containing new drugs.

Investigator

An individual responsible for the conduct of a research projects including clinical trials at a research/trial site and ensures that it complies with GCP guidelines. If a research/trial is conducted by a team of individuals at a research/trial site, the investigator is the responsible leader of the team and may be called the Principal Investigator. In this instance they may delegate tasks to other team members.

Investigator Site File (ISF)

The Investigator Site File (ISF) is the collection of essential documents which allows the conduct of a clinical trial as a site to be reconstructed and evaluated. It is basically the story of how the trial was conducted and managed at the site.

Serious breach

A breach that is serious in nature i.e. is likely to affect to a significant degree: the safety or physical or mental integrity of the participants; or the scientific value of the trial.

Sponsor

A clinical trial Sponsor is an individual, company, institution, or organization which takes responsibility for the initiation, management, and/or financing of a clinical trial. MH as sponsor for clinical trials (ICH GCP 1.53).

Trial Master File (TMF)

The trial master file (TMF) is the collection of essential documents which allows the conduct of a clinical trial to be reconstructed and evaluated. It is basically the story of how the trial was conducted and managed.

9. REFERENCES

1. Australian Code for the Responsible Conduct of Research (2018)
2. The National Statement on Ethical Conduct in Human Research, 2007 (updated 2018)
3. Safety monitoring and reporting in clinical trials involving therapeutic goods (2018)
4. MH Research Policy MH18
5. MH Documentation and Records Management Policy MH05
6. MH Research Integrity Guideline
7. MH SOP Monitor Responsibilities
8. MH Data Management in Research Guideline
9. The Integrated Addendum to ICH E6(R1): Guideline for Good Clinical Practice ICH E6 (R2) – annotated with TGA comments (Current Step 4 version, dated 9 November 2016)

7. APPENDICES

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Appendix 2: Preparing for a Monitoring Visit
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DOCUMENT END

APPENDIX 1: SOP CHANGE LOG

Date	Version	Author* and contributors Reason for issue
1/7/2019	1	Sarah Rickard First issue

Appendix 2: PREPARING FOR A MONITORING VISIT

Monitoring Visit Preparation checklist

Study Number: **Date:**

The Monitor should undertake the following activities in preparation for the on-site monitoring visit:

<This form should be tailored to the specific study and monitoring plan>

Item #	Item	Completed
1	Communicate with the CPI/PI and site staff to:	
	• notify the site of upcoming monitoring visit and the type of visit planned	
	• schedule the visit at a mutually acceptable time which fits the monitoring schedule	
	• arrange a time during the visit to meet with key team members including CPI/PI	
	• confirm the recruitment status	
	• confirm if there are any pending ethics approvals	
	• notify site staff of the required documents to be available for the visit	
2	• The Monitor should also inform the CPI of visits scheduled at Participating Sites	
3	The Monitor must liaise with the Study Coordinator to arrange access, in time for the visit and in accordance with each institution's policies, to the following documents/systems	
	• medical records – in paper, electronic or electronic scanned format and the participant research file as applicable	
	• case Report Forms - paper and/or electronic formats	
4	Complete the following in pre-visit preparation activities:	
	• Review previous monitoring documentation as available and including (i) monitoring visit reports and follow up correspondence. (ii) audit reports. (iii) annual reports to HREC. (iv) any other documents, as appropriate, that may indicate items requiring follow-up.	
	• Identify and familiarize themselves with the current approved protocol and other approved trial documents	
	• Prepare and print out monitoring tools such as checklists and reports	

APPENDIX 3: REVIEW OF INVESTIGATOR AND SITE STAFF SUITABILITY

At each monitoring visit, the Monitor should confirm the continued ability and commitment of the Investigator and site staff to conduct the trial.

This includes the following tasks:

- Verifying that the PI and site personnel are adhering to the protocol and conducting the trial within the conditions of the HREC approval and according to regulatory requirements and GCP.
- Reviewing the Delegations Log and Training Log to ensure it is complete, current and delegation is in accordance with qualifications and training and all tasks have been assigned.
- Ascertain the participant recruitment rate and determine if enrolment is adequate.

APPENDIX 4: REVIEW OF INFORMED CONSENT DOCUMENTATION

The Monitor must review all informed consent documents for participants enrolled on the trial according to the monitoring plan.

The Monitor must verify data and processes identified as critical for the integrity of data and safety of participants for all participants.

The purpose of informed consent document review is to ensure that:

- Participant inclusion and exclusion criteria-Confirm only eligible participants are enrolled
- All participants entering trial screening have provided written informed consent before any trial related procedures we recarried out;
- The consent process conforms with GCP and regulatory requirements and is consistent with the consent procedure detailed in the ethically approved protocol;
- The consent process is documented in the participant's source documents and the source data agree with the data entered in the CRF;
- Procedures and assessments related to the primary objective and other key objectives have been completed according to the protocol.

Review of Informed Consent Documentation **Study Number:** **Date:**

The Monitor must verify the following for each screened participant:

<This form should be tailored to the specific study and monitoring plan>

Item number	Item	Evidence	Comments
1	Signed participant information and consent form (PICF), including PICFs used for reconsent (if applicable), have been filed in accordance with RMH requirements: • High quality copy in the EMR, • Original in participant's research file.	Yes No	
2	Confirm that the person providing consent (i.e. participant, person responsible, MTDM) has been provided a copy of the fully signed consent form. This should be	Yes No	
3	Where the research impacts the ongoing care of the patient, verify that informed consent has been documented in the participant's medical record This should include: • date of consent, • who conducted the consent, • the name and HREC number of the trial, • the participant had the chance to ask questions and had them answered to their satisfaction, • a certified interpreter was used (if applicable) , • a contact person, • any other relevant information other members of the participant's treating team may need to know in order to conduct routine clinical care (e.g. contraindicated medicines).	Yes No	
4	The procedure used for consent, and reconsent (if applicable), is adequately recorded in the medical record and/or participant's research file (as evidence of compliance with GCP 4.8) including: • When the PICF was given to the participant for consideration, • When the informed consent discussion took place,	Yes No	

	• The date of consent and whether it was before or after the start of trial-related procedures • For reconsent –the date of consent and whether it was timely and appropriated. The current approved version of consent documents were used at time of consent (GCP 4.8.2);		
5	The participant or representative and the person taking consent have personally signed and dated the consent form (GCP 4.8.8);	Yes No	
6	In cases where the participant or representative cannot read, an impartial witness has signed and dated the consent form (GCP 4.8.9);	Yes No	
7	Date of consent correlates with a visit date, either before or on the day of the first trial-related activity SDV and CRF review.	Yes No	
8	•	Yes No	

APPENDIX 5: REVIEW OF COMPLIANCE WITH THE PROTOCOL AND APPROVED DOCUMENTS

The Monitor must review all study documentation to ensure compliance with the protocol and approved documents.

The Monitor must verify data and processes identified as critical for the integrity of data and safety of participants for all participants.

The purpose of the review is to:

(a) Ensure that the investigator and the investigator's trial staff are adequately informed about the trial.

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

(c) Verify 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.

(d) Ensure 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).

(e) Verify that the investigator is enrolling only eligible participants.

(f) Report the participant recruitment rate.

APPENDIX 6: REVIEW OF ESSENTIAL DOCUMENTATION

A list of Essential Documents is provided in Chapter 8 of the *Integrated Addendum to ICH E6(R1): Guideline for Good Clinical Practice ICH E6(R2).*

Essential documents may be maintained in the Trial Master File (TMF), the Investigator Site File (ISF) or other trial folders.

TMF - All studies, whether single and multi-centre studies, should have a TMF. The TMF is maintained by the coordinating site for investigator-initiated studies. The coordinating site is usually the site of the authors of the protocol. The coordinating site may be the CTN/CTX sponsor of

The TMF is the repository for Essential Documents that are common to all sites and the Essential Documents specific to the Coordinating Lead site.

If the trial is multi-centre, the TMF must include a Site Information File for each participating site. The Site Information File only needs to contain those Essential Documents that are specific to the site.

Participating sites in a multi-centre trial must file essential documents in an Investigator Site File (ISF). The Principal Investigator is responsible for maintaining the ISF.

The TMF/ISF should be reviewed at each monitoring visit using a checklist to document the review, record documents that are present and those that are missing. If a trial is using an electronic TMF (eTMF), the Monitor should be given access and may conduct their review within one week of the visit, either before or after.

The purpose of the Essential Document review is to ensure:

- All necessary approvals are in place prior to commencement of recruitment activities;
- Amendments, if any, are only implemented after all approvals are in place;
- The Investigator is complying with regulatory requirements in relation to provision of necessary reports in order to maintain the approvals;
- The trial has all required materials, including CRF, consent documents, training and delegation logs to ensure the proper conduct and documentation of the trial;
- The TMF/ISF identifies the trial appropriately and in an orderly fashion, and is stored securely;
- Participant confidentiality is maintained;
- The CPI/PI are maintaining sufficient oversight of the trial;
- The file is “inspection/audit-ready”. The Monitor must verify a number of items during the review of the TMF/ISF:
- Documentation of all submission and approvals to all relevant bodies are filed, including responses to questions/comments;
- Annual reports, Safety reports, notification of change to PI/Associate Investigators are submitted in specified timeframe to the approving HREC;
- The trial team is working to the latest approved protocol and has the most current information on the investigational product, such as the latest Investigator Brochure or Product Information.

Review of Essential Documentation **Study Number:** **Date:**

<This form should be tailored to the specific study and monitoring plan>

Item #	Item	Evidence	Comments
1	The TMF/ISF identifies the trial appropriately and in an orderly fashion, and is stored securely	Yes No	
2	All necessary approvals are in place prior to commencement of recruitment activities	Yes No	
3	Documentation of all submission and approvals to all relevant bodies are filed, including responses to questions/comments	Yes No	
4	Amendments, if any, are only implemented after all approvals are in place	Yes No	
5	Annual reports, Safety reports, notification of change to PI/Associate Investigators are submitted in specified timeframe to the approving HREC	Yes No	
6	The Investigator is complying with regulatory requirements in relation to provision of necessary reports in order to maintain the approvals	Yes No	
7	Reportable events have been appropriately documented and reported according to regulatory requirements, the HREC/Research Governance Office, protocol and SOPs.	Yes No	
8	The trial has all required materials, including CRF, consent documents, training and delegation logs to ensure the proper conduct and documentation of the trial	Yes No	
9	The trial team is working to the latest approved protocol and has the most current information on the investigational product, such as the latest Investigator Brochure or Product Information	Yes No	
10	Evidence of documenting and reporting of non-compliance to GCP, SOPs or protocol e.g. Note to Files, Corrective and Preventative Action Plans [CAPAs]	Yes No	

12	The delegation log is up-to-date, accurately reflects members of the study/trial team and their delegated responsibilities and all tasks have been delegated or will be undertaken by the PI	Yes No	
13	The qualifications and training (including trial-specific and GCP training) for all delegated members of the trial team is documented and valid at all times throughout the trial and for their delegated responsibilities.	Yes No	
14	The participant screening/enrolment status is accurately reflected on trial logs and consent documents.	Yes No	
15	Participant confidentiality is maintained	Yes No	
16	Participant identifiable information is not present in any documents other than the signed informed consent and the participant ID log (and not for any non-trial participant).	Yes No	
17	The latest approved versions of participant consent documents are used.	Yes No	
18	Laboratory samples, if applicable, are correctly tracked and handled.	Yes No	
19	If specific equipment is being used for the trial, maintenance and calibration records are maintained throughout the trial.	Yes No	
20	The CPI/PI are maintaining sufficient oversight of the trial	Yes No	
21	The file appears “inspection/audit-ready”. To confirm this the Monitor must verify a number of items during the review of the TMF/ISF.	Yes No	

APPENDIX 7: REVIEW OF SOURCE DOCUMENTS AND THE CRF

The purpose of reviewing source documents and the CRF is to verify accuracy and completeness of the CRF entries, source documents and other trial-related records against each other, are kept up-to-date and maintained.

Traditionally commercially sponsored clinical trials have undergone 100% source data verification (SDV). However, more recently the industry has recognised that risk-based monitoring is a time and cost-effective way to monitor studies. Further, the National Statement on Ethical Conduct in Human Research (2007) (National Statement) permits monitoring arrangements to be commensurate to the risk, size and complexity of the trial.

Completion of a study risk assessment should identify the potential risks of and to critical processes and data before initiation of a trial.

Use this information in developing the monitoring plan and to justify reduced SDV monitoring (i.e. where 100% SDV is not undertaken).

The Monitor must verify that source document requirements are met.

The monitor should review SDV and CRF to verify that:

- Protocol specified visits and procedures are conducted as specified in the protocol.
- Data required by the protocol are collected and reported accurately and legibly on the CRF in timely manner and are consistent with the source documents.
- Any dose and/or therapy modifications are well documented for each of the trial participants.
- All reportable events (including adverse events, concomitant medications and intercurrent illnesses) are documented and reported in accordance with the protocol and applicable requirements.
- Visits that the participants fail to make, tests that are not conducted, and examinations that are not performed are clearly reported as such on the CRFs.
- All withdrawals and dropouts of enrolled participants from the trial are reported and explained on the CRFs.
- Any non-compliance to the protocol is identified and reported appropriately.

Where the monitor identifies any CRF entry error, omission, or illegibility. The monitor should inform the investigator (or delegate) and 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 authorised to initial CRF changes for the investigator. This authorisation should be documented.

APPENDIX 8: REVIEW OF INVESTIGATIONAL PRODUCT MANAGEMENT (IP)

For studies involving IP, monitoring of IP documentation (including Pharmacy records) should be conducted in accordance with the study monitoring plan.

IMPORTANT NOTE for blinded clinical trials: where monitoring the IP has the potential to unblind the monitor, the IP management review cannot be undertaken by the same person who undertakes essential document review, including signed informed consent. In this case a separate unblinded monitor should be used.

The purpose of IP management review is to ensure that:

- Investigator/delegate has relevant and updated information on the IP, such as current Investigator's Brochure or commercially available Product Information;
- IP is handled as per manufacturer's instructions and protocol requirements;
- IP handling is only performed by delegated and appropriately trained staff.
- Participant compliance with prescribed IP dose and instructions for use.

The Monitor must verify:

- Appropriate documents are present pertinent to safety information of the IP, including Investigator Brochure (IB)/Product Information;
- Staff carrying out IP-related activities are listed on the Delegation and Training Logs and have been appropriately delegated/trained;
- The IP is stored in accordance with trial IB/Product Information and there is sufficient stock to supply participants in accordance with anticipated recruitment rate and IP dose;
- Shipping documents are present if IP was sent from manufacturer/Sponsor, such as shipping logs, downloaded temperature logs;
- Temperature excursions (during both shipment to site and storage on site) are correctly documented and escalated appropriately, and affected investigational product stock is correctly handled and documented;
- The IP is correctly dispensed according to protocol requirements and for enrolled patients only, including randomisation if applicable;
- Masking of treatment is maintained if applicable;
- IP accountability records confirm records of receipt, dispensing and disposition and are current and accurate;
- There is sufficient quantity of IP within expiry date on site for continuation of trial.
- Appropriate documentation is in place for any return or destruction of stock, such as shipment confirmation, destruction certificate.
- That participants are provided with necessary instruction on properly using, handling, storing, and returning the IP(s).
- Participant diary records reconcile with pharmacy dispensing records – This would be done for a pre-specified number/percentage of participants and as identified in the monitoring plan.

APPENDIX 9: REVIEW OF ADVERSE EVENT REPORTING DOCUMENTATION

The purpose of reviewing AE reporting documentation is to:

- Verify 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.

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

- Confirm information regarding AEs has been communicated to the participants involved and if required to all participants on the study.

- Confirm that the investigator has implemented appropriate action designed to prevent recurrence of the detected AE where possible.

The monitor should undertake a full review of the event, documentation and expedited reporting.

The monitor must verify the following data for a proportion of participants commensurate to the risk of the trial and as identified in the Monitoring Plan:

- Adverse Events – Confirm there is there evidence of review of AEs at each trial visit, and information on AEs have been documented, including but not limited to onset/offset date, relationship to investigational product, any concomitant medications taken?
- Investigational product administration – Confirm that the source documents agree with the data entered in the CRF, including dates and doses of trial drug/device administration.
- Participant withdrawals – Confirm that the source documents agree with the data entered in the CRF including date of visit, reason for early withdrawal and plan for future management.
- Communication with participants – Confirm that participants were followed up and informed of any risks to safety/well-being and required actions/treatments required as a result of the AEs etc. Look for documentation (e.g. emails, phone call records) to support the communication of this information with participants.
- Implementation of Preventative action – Confirm that implementation of appropriate preventative actions has been documented if applicable i.e. the AE was a result of an error in the protocol/a procedure. Documentation may include amendments to the protocol/participant information, notes to file, training of study team etc.

APPENDIX 10: Research sample/Laboratory Management Review

Monitoring of laboratory and sample management should be carried out according to the risk of the trial and the endpoints that the sample analysis supports (for example, primary pharmacokinetic endpoints or exploratory translational endpoints).

The purpose of sample/laboratory management review is to ensure that:

- Research samples are collected, processed and stored appropriately according to protocol and trial requirements
- Movement of samples are in accordance to protocol and laboratory manual
- Long-term storage of samples is carried out according to HREC approval.
- The Monitor should verify that:
- Samples are collected and stored only for participants who have given consent
- Participant's request for samples to be destroyed are carried out
- Accurate records of samples collected, processed and storage location are kept
- Samples are stored in appropriate temperature-monitored locations
- Any temperature excursions are reported and documented, and appropriate actions taken
- Sample shipments are documented.
- Records of relevant calibration/maintenance records are available for equipment where appropriate

APPENDIX 11: Monitoring Visit Report and Follow-up Activities

The monitoring visit report and follow up letter should be completed within 10 working days of the visit.

The monitoring visit report will be provided to the PI (for single site studies) or the CPI (for multi-site studies).

The monitoring visit report must clearly document all the activities completed and any findings from the monitoring visit and actions required.

The findings must be summarised in the correspondence (letter or email) that accompanies the report.

A copy of the Monitoring Report together with the follow up letter, attached documents and email confirming date sent must be filed in the TMF and investigator site file.

At a minimum, the following information is expected to be listed in the monitoring visit report and follow up letter:

- Recruitment status update (Open –not recruiting, Open –recruiting, Closed -Active etc.)
- Recent or upcoming amendments and approval status;
- Missing documents from the TMF/ISF review;
- Issues on delegation, training of staff and related documentation, such as CV, GCP training, trial-specific training;
- Issues on compliance with submission of annual reports and other communication with HREC, TGA and CPI;
- Non-compliance to protocol, GCP or SOPs;
- Issues noted in relation to the consent process and documentation;
- Issues with safety reporting;
- Issues with trial source data and CRF;
- Issues with investigational product management and documentation;
- Issues noted on samples/laboratory management;
- Outstanding actions from previous monitoring visits;
- Whether conduct of trial results in change in monitoring frequency or requirement.

Monitoring report must clearly list all items for follow up with recommended actions in order to assist trial team to complete issues identified.

At a mutually agreed time, or 4 to 6 weeks post visit, whichever is earlier, the monitor and site staff contact will discuss all resolved, in process and pending action items.

APPENDIX 12: Remote Monitoring

Remote monitoring activities will be restricted to the types of information the monitor can access remotely such as the CRF and/or eCRF reports and eTMF.

Remote monitoring will also be dependent on the study recruitment status and requirements detailed in the Monitoring Plan.

At all times during remote monitoring the participants privacy must be maintained.

1. Remote monitoring using eCRF

   For multisite studies using eCRF, automated statistical monitoring may be used as a method of remote monitoring. In accordance with ICH E6 (R2) (refer to Section 5.18.3), remote monitoring must be done in a timely manner and be supported by appropriately qualified staff. If remote monitoring identifies issues that cannot be resolved with the site by email or phone, or if significant issues are identified, a For-Cause visit may be justified.

2. Remote review of Informed Consent Document

   Completed consent forms can be emailed to the Monitor.

   IMPORTANT NOTE: As participant/Next of Kin (NOK)/Medical Treatment Decision Maker (MTDM) names and signatures are on completed consent forms, scanned copies sent to the Monitor must be redacted.

   All participant/NOK/MTDM names and signatures **must be** blacked out and replaced with the trial participant/screening number prior to forwarding to the monitor.

   Each form is then checked to verify that:

   - The correct and approved version of consent documents were used at time of consent;
   - The participant (NOK/MTDM) or and the person taking consent personally signed and date the consent form;
   - Date of consent correlates with a visit date;
   - Re-consent process and documentation is timely and appropriate if applicable.
   - Review of Recruitment and Retention – the monitor should obtain regular updates from site(s) regarding number of participants in the following categories:
     - Recruited
     - Non-eligible
     - Eligible but did not provide consent (with summary of the reason if available)
     - Withdrawn
     - Completed

APPENDIX 13: REVIEW OF AUTOMATED STATISTICAL MONITORING REPORTS

This review may be used for studies that use an eCRF that allows automated reports to be generated in real-time or at specified times (i.e. monthly) to inform the study team of pertinent data.

For multisite studies using eCRF, automated statistical monitoring may be used as a method of remote monitoring. In accordance with ICH E6 (R2) (refer to Section 5.18.3), remote monitoring must be done in a timely manner and be supported by appropriately qualified staff. If remote monitoring identifies issues that cannot be resolved with the site by email or phone, or if significant issues are identified, a For-Cause visit may be justified.

The monitor should review eCRF automated reports to:

- Identify missing data, inconsistent data, data outliers, unexpected lack of variability.
- Identify sites with a higher frequency of serious breaches, protocol deviation sand screen failures Case Report Form Completion Use an electronic CRF tracking form to check/track the following:
    - Received in a timely manner
    - Completeness of reporting
    - Completed by authorised personnel
    - Timely response to data queries
- Regular teleconference calls and/or emails with sites exchanging information and monitor feedback on the following:
    - Staffing –changes in personnel, training.
    - Other important hazards that require remote monitoring should be identified from the trial-specific risk assessment.

APPENDIX 14: CLOSE OUT MONITORING VISIT ACTIVITIES

The purpose of the Close-Out Visit is to ensure that all clinical trial-related activities are appropriately reconciled, recorded and reported in accordance with the protocol, SOPs, GCP and applicable regulatory requirements.

1. Close-Out Visit Approach

   Close-out visits will be conducted at participating sites once all participants have completed the trial, including long-term follow-up, all data queries are resolved, and the coordinating site has provided all required documents for inclusion in the ISF. Close-out visit will be conducted at the CPI's site once all participating sites have been closed, all participants recruited at the lead site have completed long-term follow up, data queries at the coordinating site are resolved and the site staff deem the TMF/ISF to be complete. Trial close out monitoring must be completed for all clinical trials of investigational products that have obtained/received investigational product, even if no participants were recruited. Depending on the trial, participating site closure may be via:

   - Telephone conference and remote monitoring; or
   - On-site visit – all clinical trials with investigational product supplied by MH must have an on-site Close-Out Visit.

2. Close-Out Visit Preparation

   The monitor will confirm with the trial team and the Investigator, the scope, format and anticipated duration of the close-out visit and schedule the time. The monitor will request access to the electronic and hardcopy TMF, ISF, and other relevant files (e.g. Pharmacy Manual, Laboratory Manual).

   In addition, the monitor should complete the following in preparation for the monitoring visit:

   - Review previous Monitoring Visit Reports and follow up correspondence, or audit reports, and annual reports to approving HREC, together with any other documents that may indicate items requiring follow-up.

3. Close-Out Visit Activities.

   At the Close-out Visit, the monitor must verify the following:

   - All documents, including documents maintained by other departments, are filed in the appropriate trial file (paper and or electronic), and file notes are present to provide explanation for missing documents.
   - Confirm that all reports have been submitted as required.
   - All data queries resolved;
   - Source data filed appropriately;
   - Investigational product accountability completed, including return/destruction of investigational product provided specifically for use in the trial.
   - The PI is aware of the following ongoing commitments:

- TMF (including the Pharmacy file and TMF copy of participating site ISFs) to be archived following Close-out Visit.
- Ongoing archiving arrangements.
- The Sponsor via MH OFR must be notified of all trial publications and these filed/archived as appropriate.
- All participating sites to be closed-out fully and appropriately.
- Manage the research samples long term storage or destruction according to the protocol and ethics approval.
- Responsibilities of site staff in the event of an audit in the future.

- Participating PIs are aware of the following ongoing commitments:
  - ISF to be archived following Close-out Visit. Monitor to confirm archiving arrangements and retention period.
  - The Sponsor via MH OFR must be notified of all trial publications and these filed/archived as appropriate.
  - Responsibilities of site staff in the event of an audit in the future.
- End of trial reports are/will be submitted and filed. Note: The PI should ensure that the clinical trial reports in marketing applications meet the standards of the ICH Topic E3 Note for Guidance on Structure and Content of Clinical Trial Reports, (CPMP/ICH/137/95).
- There is a procedure for archiving study materials.
- The archiving method to be used is appropriate to the type(s) of information generated in during the study (i.e. paper, electronic, video, film etc.).
- The following end of trial notifications have been submitted by the PI to, and subsequent acknowledgement of receipts from:
  i. The approving HREC.
  ii. Local Governance Office of Accepting Sites – For multi-site studies, the CPI/PI must provide accepting sites with a copy of the Final Report for submission to their local governance office.
  iii. TGA – For CTN/CTX studies, notification of completion of the clinical trial should be made only after the trial has been completed at all sites and filed in the relevant section of the TMF/ISF and a copy provided to participating sites for inclusion in their ISF.

4. Post Close-Out Visit Activities

   The Monitor must perform the following duties:

   - Complete a Close-Out Monitoring Report and follow the review process detailed in Section.
   - Send a close-out visit follow-up email and a copy of the signed report to the CPI/PI. Request the CPI/PI files the email and report in the TMF.

APPENDIX 15: FOR-CAUSE MONITORING VISITS

A For-Cause visit is a monitoring visit in response to alleged non-compliance with the protocol that may have an impact on participant safety and/or integrity of the trial data.

MH (as RGO), the approving HREC or PI may request a for-cause monitoring visit if any of the following occur

- Continual documented accounts of possible noncompliance.
- Continual documented accounts of data discrepancies.
- Proof of fraud relating to clinical trial records or data.
- Persistent or systematic non-compliance with GCP or protocol that has a significant impact on the integrity of trial participants or the scientific value of the trial.
- Failure to control investigational product(s) such that trial participants or the public are put at significant risk or the scientific value of the trial is compromised.
- Failure to report SAEs, SSIs, USMs or SUSARs in accordance with the legislation such that trial participants or the public are put at significant risk.
- Concerns over the ethical conduct of the trial by the investigator. The items reviewed in a for-cause visit are the same as those reviewed in routine monitoring visits.

The Monitor must follow the same process for monitoring and providing feedback to the site as described for routine monitoring visits.