

**Title: Standard Operating Procedure (SOP) Monitoring Visit Activities for Clinical Trials of Investigational Products**

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This document is effective from the date of the last approval signature and will be reviewed in two years.

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### 1. PURPOSE

To provide the rationale and procedures for monitoring Investigator-initiated clinical trials of investigational products (drug or device) performed where the Principal Investigator (PI), or Coordinating Principal Investigator (CPI) in the case of a multi-centre study, is an employee of the Melbourne Children’s Campus.

This SOP can be used as guidance for non-investigational drug/device clinical studies where monitoring is required at the discretion of either the Sponsor-Investigator or the approving HREC or Research Governance Office.

The purpose of clinical trial monitoring is to verify that:

- The Investigator is conducting the study in accordance with the protocol, Good Clinical Practice (GCP) guidelines and applicable regulatory requirements;
- The Investigator and members of the study team are appropriately trained and supported to complete their role in the study;
- The participant's safety, rights and well-being are protected; and
- Data recorded on the case report forms are accurate, complete and verifiable from source documentation.

The Sponsor should determine the appropriate extent and nature of monitoring using a risk-based assessment informed by considerations such as the objective, purpose, design, complexity, blinding, size, and endpoints of the trial.

## 2. RESPONSIBILITY AND SCOPE

This SOP applies to all Melbourne Children's Campus staff who undertake the following roles associated with investigator-initiated trials sponsored by MCRI:

- Sponsor-Investigator
- PI
- Monitor

For all single-site Investigator-initiated trials and multi-site IITs sponsored by MCRI, the PI/CPI must assume the role of Sponsor with regards to ensuring the trial is adequately monitored as defined by GCP, Section 5.18 Monitoring.

This SOP uses the following terminology to distinguish between the CPI's/PI's role as Sponsor and local Principal Investigator at the lead site:

Sponsor-Investigator – used when referring to Sponsor responsibilities

Coordinating PI/PI – used when referring to responsibilities at site level (multi- centre and single centre, respectively).

This SOP applies to all preparation, conduct and follow-up of monitoring activities. Monitoring activities include site initiation visits, routine monitoring visits, remote monitoring, close-out visits and for-cause visits.

### 2.1. Sponsor-Investigator

The Sponsor-Investigator is responsible for appointing a Monitor or team of Monitors in accordance with GCP, Section 5.18.2. An External Monitor may be contracted to carry out all or a proportion of monitoring activities. External monitors may monitor according to their own company's SOPs.

### 2.2. Monitor(s)

Responsibilities of the Monitor(s) include:

- Verifying adherence to GCP guidelines
- Monitoring adherence to the HREC-approved protocol and reporting serious breaches to the Sponsor-Investigator.
- Performing site initiation visits
- Assisting sites with logistical issues as needed
- Performing routine monitoring visits as defined in Section **Error! Reference source not found.**, which would include:
  1. Evaluating the progress of the study, including such factors as:

- a. Periodic assessments of data collection, recording, and submission timelines
  - b. Performing investigational product accountability
  - c. Ensuring that participant rights are protected by verifying informed consent
- 2. Making recommendations to the Investigators and Sponsor-Investigator regarding data discrepancies, improvements in compliance, participant recruitment progress, and retention methods
- 3. Ensuring that Significant Safety Issues (SSIs), Suspected Unexpected Serious Adverse Reactions (SUSARs) and Serious Adverse Events (SAEs) (or Serious Adverse Device Effects [SADEs], Unexpected SADEs [USADEs] for device trials) are reported to all required stakeholders [e.g., HREC, RGO, Sponsor, Investigators, Data and Safety Monitoring Boards (DSMBs) and TGA] in accordance with the protocol and individual stakeholder requirements
- Assisting the PI and study team in the preparation for any potential governance/regulatory audit(s)

### **2.3. Coordinating Principal Investigator/Principal Investigator and Study Team**

During a monitoring visit, the CPI/PI/delegate is responsible for providing direct access to all relevant study-related records including:

- Study data in CRFs (electronic or paper)
- Source documents, such as:
  1. Patient medical records
  2. Laboratory results and diagnostic reports
  3. Other applicable source documentation (e.g., patient diaries, vital signs)
  4. Consent documents
  5. Screening documents
  6. Other study-specific documents as necessary
- Regulatory file/Investigator Site File
- Drug accountability records, which may necessitate a pre-arranged appointment with clinical trials pharmacy or other Institutional Pharmacies
- Laboratory specimen collection, processing, storage, and shipment records

The CPI/PI and/or delegate should be available at the start of the monitoring visit for set-up questions and at the conclusion for a summary of site visit findings. The site Study Coordinator (SC) or delegate should be available, as needed, to meet with the Monitor during the visit.

## **3. PROCEDURE**

### **3.1. General Approach**

The Monitor should follow a study-specific Clinical Monitoring Plan (CMP) based on the level of risk involved in the trial. The CMP should be completed prior to site initiation. Please refer to CRDO's CMP template for further guidance.

The frequency of interim on-site monitoring visits will depend on the rate of participant recruitment and the complexity of the study, but should occur at least annually.

Onsite visits should be conducted before, during and after the trial.

The first interim monitoring visit should be scheduled as soon as possible, preferably within 6-8 weeks after the first participant receives the intervention. However, the Sponsor-Investigator may reduce the need for onsite visits using centralised (remote) monitoring together with additional procedures (such as Investigator training, regular meetings, and extensive written guidance, e.g. SOPs) to give assurance of appropriate conduct in accordance with GCP. For-cause visits may be conducted at an individual site if a serious breach (breach that 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) has occurred.

Monitoring should continue until the last participant has completed follow-up evaluations according to the protocol.

### **3.2. Site Initiation Visit**

Fiona, Natalie and Carolyn: Consider removing SIV from SOP as not really a monitoring activity but a training activity. Also for IIT trials, training is responsibility of clinical trial/research team, not the Monitor.

#### **3.2.1. SIV Preparation**

The Site Initiation Visit (SIV) cannot occur until site set up is complete and the trial has been registered on a primary register of the WHO International Clinical Trials Registry Platform (ICTRP) or ClinicalTrials.gov. Refer to CRDO's Standard Operating Procedure, "Clinical Trial Registration of Investigator-Initiated Trials (IITs)", to ensure you fulfil the registration requirements for your trial.

The following activities should be completed by the Monitor when preparing for a SIV:

- Verify ethics and governance approval and TGA acknowledgement of receipt of Clinical Trial Notification (CTN), if applicable. This may require the local site Study Coordinator to send PDF versions of documents to the Monitor.
- Liaise with the CPI/PI and site staff to schedule the visit. Notify the CPI (Sponsor-Investigator) of visit scheduling at Participating Sites.
- Verify all supporting departments are set up to start study, including finalisation of applicable guidance documents such as Pharmacy Manual, laboratory manuals etc.
- Verify arrangements in place for supply of investigational products
- Verify study documents are in place for study to commence recruitment
- Verify adequate supply of all materials required to conduct study in accordance with the protocol

#### **3.2.2. SIV On-Site Activities**

The following activities should be completed during an onsite SIV to ensure that the CPI/PI, staff, and facility are ready to commence the trial:

- Provide training to CPI/PI and applicable site staff regarding:
  - Current protocol and/or amendments
  - Study timeline and enrolment expectations
  - Case report form completion, correction and submission procedures, including study-specific monitoring conventions

- Protocol deviations and serious breaches
  - Source document verification (SDV)
  - Investigator Brochure (IB) (if applicable)
  - Informed consent obligations
  - Enrolment/randomisation/treatment assignment/blinding procedures
  - Safety reporting
  - Study manual/Standard Operating Procedures (SOPs)
  - Supplying and handling investigational products
  - Pharmacy manual
  - Investigator site file (study binder)
  - Human Research Ethics Committee and Governance requirements
  - Laboratory requirements
  - Investigator obligations
  - Monitoring visits
  - Audits
  - Record retention
  - Publication policy
  - Once all the above has been discussed, review the Delegation Log and Training Log to ensure it is complete, current and delegation is in accordance with qualifications and training.
- Inspection of site facilities must include the following:
    - Treatment prepared in a location and manner that avoids unblinding or cross-contamination
    - Adequate facilities for storage of investigational agents, placebos and laboratory specimens that will be stored for testing at a later date
    - Adequate facilities for all study-related procedures
    - Verification that the electronic Trial Master File (TMF)/Investigator Site File (ISF) has restricted access to members of the study team
    - Verification that site has received all supplies required to conduct the study, e.g. investigational product, manuals, paper CRFs (if using), ISF study binders (if using paper), laboratory supplies
  - Monitoring Visit Log must be signed

### **3.2.3. Post SIV Follow-up**

The following activities should be performed upon completion of a SIV:

- SIV findings and resulting action items must be documented in a Site Initiation Visit Report. The Monitor will complete a report and provide a follow up email to the CPI/PI and site staff within 10 business days of the visit.
- The Monitor should assist site staff to resolve outstanding action items as communicated in the follow-up email within 4-6 weeks post visit.

### **3.3. Routine Monitoring Visits**

### 3.3.1. Monitoring Visit Preparation

The Monitor should liaise with the CPI/PI and site staff to schedule the visit, arrange a time to meet with key team members including CPI/PI, and notify site staff of the required documents for the visit. The Monitor should also inform the Sponsor-Investigator of visit scheduling at Participating Sites.

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:

- the hardcopy or electronic medical record / electronic scanned medical record and/or the participant shadow file (Refer to glossary for definition)
- the paper and/or electronic Case Report Forms.

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

- Review previous monitoring visit reports and follow up correspondence, if available, or audit reports and annual reports to HREC, together with any other documents that may indicate items requiring follow-up;
- Become familiar with the current approved protocol;
- Check with trial team regarding recruitment status, any pending ethics approvals etc.
- Prepare and print out monitoring tools such as:
  1. Copy of previous TMF/ISF checklist (Refer to template TMF/ISF checklist in Appendix X)
  2. Current list of safety reports as follows:
    - a. Sponsor – Investigator site - safety reports to participating site Investigators/Approving HREC/TGA and local RGO (SSIs, local USMs and local SUSARs only) (Contact MCTC for further details)
    - b. Participating sites - safety reports to Sponsor-Investigator and RGO (Contact MCTC for further details)
  3. Current eCRF validation report for inconsistent data, missing data, range checks, and deviations from the protocol
  4. Blank Monitoring Visit Report template (electronic and/or paper)

### 3.3.2. Monitoring Visit On-Site Activities

Monitoring activities to be completed at each on-site visit will depend on the recruitment status (Open – not recruiting, Open – recruiting, Closed – Active not recruiting, Closed – Completed) and requirements detailed in the Clinical Monitoring Plan. At a minimum, the Monitor must:

- Review outstanding items for follow-up from previous activities to check for completion;
- Assess protocol adherence and compliance with protocol, GCP, institutional policies and regulatory requirements;
- Review essential documents (TMF/ISF) for accuracy and completeness;
- Review completed informed consent documents;
- Conduct source document verification (SDV) and CRF review;
- Review investigational product records (drug/device accountability);
- Review Investigator and site staff suitability,
- Review recruitment/retention
- Sign the Monitoring Visit Log

### ***Essential Documents review***

According to ICH GCP, Essential Documents are those “documents which individually and collectively permit evaluation of the conduct of a study and the quality of the data produced”.

There are up to three types of files for maintaining Essential Documents in a study as described below.

All studies, single and multi-centre, must have a Trial Master File (TMF) that is maintained by the Sponsor-Investigator. 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 study 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 study must file essential documents in an Investigator Site File (ISF). The Principal Investigator is responsible for maintaining the ISF.

MCRI’s Clinical Research Development Office provides guidance documents for maintaining essential documents for single centre studies and multi-centre studies for campus-led Investigator-Initiated Trials. Please refer to the following guidance documents accessed via the CRDO website at <https://www.mcric.edu.au/research/training-and-resources/clinical-research-development-office-crdo/resources-quantitative>: “STUDY BINDERS - Guidelines, table of contents and section detail” and “PARTICIPATING SITE STUDY BINDERS – Instructions for Coordinating Lead Sites”.

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. Templates for a TMF Review Checklist and Participating Site ISF Checklist are available via the CRDO website at <https://www.mcric.edu.au/research/training-and-resources/clinical-research-development-office-crdo/resources-quantitative>. If a study 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 Sponsor-Investigator and 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;
- Evidence (e.g. Note to Files, Corrective and Preventative Action Plans [CAPAs]) of documenting and reporting of non-compliance to GCP, SOPs or protocol;
- The delegation log is up-to-date, accurately reflects members of the trial team and their delegated responsibilities and all tasks have been delegated or will be undertaken by the Sponsor-Investigator/PI;
- 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;
- Reportable events have been appropriately documented and reported according to regulatory requirements, the HREC/Research Governance Office, protocol and SOPs;
- The participant screening/enrolment status is accurately reflected on trial logs and consent documents;
- 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);
- The latest approved versions of participant consent documents are used;
- Laboratory samples, if applicable, are correctly tracked and handled;
- If specific equipment is being used for the trial, maintenance and calibration records are maintained throughout the trial.

#### ***Informed Consent Documents review***

The Monitor must review all informed consent documents for all participants enrolled on the study.

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

- All participants entering trial screening have provided written informed consent before any trial related procedures were carried out;
- The consent process conforms with GCP and regulatory requirements and is consistent with the consent procedure detailed in the protocol;
- The consent process is documented in the participant's source documents; this will be checked in line with SDV and CRF review requirements as stipulated in the formalised Clinical Monitoring Plan document. *(Please refer to CRDO Clinical Monitoring Plan template for guidance on how to set up a Clinical Monitoring Plan).*

The Monitor must verify the following for each screened participant:

- a. Signed informed consent forms and accompanying participant information statement (PICF), including PICFs used for re-consent (if applicable), have been filed in accordance with RCH Health Information Services' recommendations as follows:
  - High quality copy or original in the EMR
  - Original in participant's shadow file

Note: The participant/parent/guardian should have also been given a copy
- b. Where the research impacts the ongoing care of the patient, verify that informed consent has been documented in the participant's medical record in accordance with RCH Research Policy, Informed Consent in Research, Section 4.11 as outlined below:

*"If the research impacts the ongoing clinical care of the patient, i.e. if the treating team needs to be aware that the patient involved in research, then the consent process must be documented. This should include: date of consent, who conducted the consent, the name and HREC number of the trial, a certified interpreter was used (if applicable) and*

*contact person and any 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).*

*For high risk trials the researcher must associate the patient to the research project within the electronic medical record.”*

- c. The procedure used for consent, and re-consent (if applicable), is adequately recorded in the medical record or participant’s shadow 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
  - The date of consent and whether it was before or after the start of trial-related procedures
  - For re-consent – the date of consent and whether it was timely and appropriate
- d. The current approved version of consent documents were used at time of consent (GCP 4.8.2);
- e. The participant or parent/guardian and the person taking consent have personally signed and dated the consent form (GCP 4.8.8);
- f. In cases where the participant or parent/guardian cannot read, an impartial witness has signed and dated the consent form (GCP 4.8.9);
- g. Date of consent correlates with a visit date, either before or on the day of the first study-related activity

#### ***SDV and CRF review***

The percentage of SDV and CRF review to be completed for each trial is determined by risk assessment of the trial and the trial team experience and should be documented in the study-specific Clinical Monitoring Plan.

The purpose of SDV and CRF review is to ensure that:

- Data collected on the CRF is entered in a legible and timely manner;
- Data collected is accurate and consistent with source documents;
- Any erroneous/missing data identified during SDV and CRF review is corrected/resolved in a timely manner;
- Protocol specified visits and procedures are conducted as specified in the protocol;
- Any non-compliance to the protocol is identified and reported appropriately;
- All reportable events are documented and reported.

The Monitor must verify that source document requirements are met (Note these should be documented in a Source Document Plan. Please refer to CRDO website for a sample template at the following location: <https://www.mcri.edu.au/research/training-and-resources/clinical-research-development-office-crdo/resources-quantitative> ).

At a minimum, the Monitor must verify data and processes identified as critical for the integrity of data and safety of participants for all participants. This includes, but is not limited to, the following:

- **Participant inclusion and exclusion criteria** -Confirm only eligible participants are enrolled.
- **Informed Consent** - Has this been completed as defined in Informed Consent Documents Review?
- **Procedures and assessments related to the primary objective and other key objectives**, – Do the source data agree with the data entered in the CRF?

- **SAEs/SUSARs/USMs** – 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 study and as identified in the Clinical Monitoring Plan:

- **Adverse Events** – 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** – Do the source documents agree with the data entered in the CRF, including dates and doses of trial drug/device administration?
- **Participant withdrawals** – Do 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** – Does the documentation (e.g. emails, phone call records) reveal any important information related to the safety/well-being of the participants?

#### ***Investigational Product Management Review***

Monitoring of Pharmacy will be carried out according to trial-specific monitoring plans. These details will be captured in the trial-specific Clinical Monitoring Plan.

Note that in the case of blinded clinical trials, if monitoring the investigational product has the potential to unblind the Monitor, the investigational product 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. Please refer to “Clinical Monitoring Plan – Unblinded monitoring of investigational product” for further details regarding monitoring investigational product in blinded studies.

The purpose of investigational product management review is to ensure that:

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

The Monitor must verify:

- Appropriate documents are present pertinent to safety information of the investigational product, including Investigator Brochure/Product Information;
- Staff carrying out investigational product-related activities are on the Delegation and Training Logs and have been appropriately delegated/trained;
- The investigational product is stored in accordance with trial Investigator Brochure/Product Information and there is sufficient stock to supply participants in accordance with anticipated recruitment rate and investigational product dose;
- Shipping documents are present if investigational product 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 investigational product is correctly dispensed according to protocol requirements and for enrolled patients only, including randomisation if applicable;

- Masking of treatment is maintained if applicable;
- Investigational product accountability records confirm records of receipt, dispensing and disposition and are current and accurate;
- There is sufficient quantity of investigational product 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.
- 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 Clinical Monitoring Plan.

### ***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

### ***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 study. This includes the following tasks:

- Verify that the PI and site personnel are adhering to the protocol and conducting the study within the conditions of the HREC approval and according to regulatory requirements and GCP.
- Review 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.

### **3.3.3. Post Monitoring Visit Follow-up**

Report and follow up letter should be completed within 10 working days of the visit. The report must clearly document all the activities completed and any findings from the monitoring visit. Please contact CRDO to request a Monitoring Visit Report template.

Unlike trials sponsored by external companies (Pharma and collaborative groups), the monitoring report will be provided to the PI/CPI. The report must clearly record all findings and actions required. Findings which cannot be reported in appropriate sections in the report are recorded in a general comments section. The findings must be summarised in the correspondence (letter or email) that accompanies the report.

A copy of the Monitoring Visit 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.

### **3.4. Remote Monitoring**

Remote monitoring activities will depend on the recruitment status, requirements detailed in the Clinical Monitoring Plan and if the Monitor has access to the eCRF and/or eCRF reports and eTMF. Monitoring activities that may be done remotely include:

#### ***Review of Consent Forms***

Within a pre-defined timeframe following consent and detailed in the Clinical Monitoring Plan, completed consent forms can be emailed to the Monitor. As participant/parent/guardian names and signatures are on completed consent forms, scanned copies sent to the Monitor must be redacted.

All participant/parent/guardian names and signatures must be blacked out and replaced with the study participant/screening number.

Each form is then checked to verify that:

- The correct and approved version of consent documents were used at time of consent;
- The participant 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***

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)
- Withdrawn

### ***Statistical Monitoring***

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 deviations and 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

### ***Other***

- 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 study-specific risk assessment.

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 by email or phone, or if significant issues are identified, a For-Cause visit (see section 3.7) may be justified.

Feedback outcome of remote monitoring activities to CPI/PI and site staff using a Remote Monitoring Visit Report template. Note: CRDO is has plans to develop a Remote Monitoring Visit Report template. Please contact CRDO department to establish availability.

### **3.5. Close-Out Visit**

#### **3.5.1. Purpose**

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.

#### **3.5.2. Close-Out Visit Approach**

Close-out visits will be conducted at participating sites once all participants have completed the study, including long-term follow-up, all data queries are resolved and the Coordinating Lead site has provided all required documents for inclusion in the ISF.

Close-out visit will be conducted at the Sponsor-Investigator'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 lead 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 study, participating site closure may be via:

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

#### **3.5.3. Close-Out Visit Preparation**

The Monitor will confirm with the trial team and the Sponsor-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;
- Prepare and print out monitoring tools such as:
  1. Copy of previous TMF/ISF checklist;
  2. Blank Close-Out Visit Report template

#### **3.5.4. 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, and file notes are present to provide explanation for missing documents;

- The following end of trial notifications, and subsequent acknowledgement of receipts, have been submitted by the PI/Sponsor-Investigator to:
  - Approving HREC – When RCH HREC is the approving HREC, please use RCH Final Report Form (available from RCH REG website) or the NMA HREC Final Report Form available at the following link: <https://www2.health.vic.gov.au/about/publications/researchandreports/hrec-final-report>
  - Local Governance Office of Accepting Sites – Sponsor-Investigator must provide accepting sites with a copy of the Final Report for submission to their local governance office.
  - TGA - Notification of completion of a 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.

- End of trial reports are/will be submitted and filed. Note: The PI/Sponsor-Investigator 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 Study Reports, (CPMP/ICH/137/95).
- 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 Sponsor-Investigator 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. Monitor to confirm archiving arrangements.
  - The Sponsor / MCRI 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 / MCRI 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.

### **3.5.5. 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 3.3.3.
- 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.

### **3.6. For-Cause Visit**

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.

MCRI, the approving HREC or the Sponsor-Investigator 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 study 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 in Section 3.3.3.

#### **4. GLOSSARY**

##### **Adverse Event (AE)**

Any untoward medical occurrence in a patient/clinical trial participant administered a medicinal product and does not necessarily have a causal relationship with the treatment.

##### **Adverse Device Effect (ADE)**

Adverse event related to the use of an investigational medical device.

##### **Adverse Drug Reaction (ADR)**

Any untoward and unintended response to an investigational medicinal product related to any dose administered. A causal relationship between the medicinal product and the response is *at least* a possibility.

##### **Audit**

A systematic and independent examination of trial-related activities and documents to determine whether the trial related activities were conducted, and the data were recorded, analysed and accurately reported according to the protocol, sponsor's standard operating procedures (SOPs), Good Clinical Practice (GCP), and the applicable regulatory requirements.

##### **Clinical Research Organisation**

An organisation - commercial, academic, or other - contracted by a Sponsor to perform one or more of the Sponsor's clinical trial-related duties and functions.

##### **Coordinating Site Lead Principal Investigator (CPI)**

The Investigator who is the lead PI on a multi-centre investigator initiated clinical study. They will also be the principal point of contact between the groups of collaborating investigators/researchers and the approving HREC for a multi-centre ethics approval.

##### **Case Report Form (CRF)**

A printed, optical, or electronic document designed to record all of the protocol required information to be reported to the Sponsor on each trial participant.

##### **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.

**Delegate**

A person delegated specific but appropriate QA tasks in relation to the study.

**Essential Documents**

Those documents which individually and collectively permit evaluation of the conduct of a study and the quality of the data produced.

**Governance Office**

The Office or coordinated function within a Public Health Organisation which is responsible for assessing the site-specific aspects of research applications and overseeing that authorised research at the site meets appropriate standards (research governance).

**Human Research Ethics Committee (HREC)**

An institutional body that has been established in accordance with Chapter 5.1 of the NHMRC/ARC/AVCC *National Statement on Ethical Conduct in Human Research* and conducts the ethical review of research. Under the national approach, a single HREC conducts an ethical review that is accepted by multiple institutions. HRECs play a central role in the Australian system of ethical oversight of research involving humans. HRECs review research proposals involving human participants to ensure that they are ethically acceptable and in accordance with relevant standards and guidelines.

**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.

**Investigational Medical Device (IMD)**

Medical device being assessed for safety or performance in a clinical investigation. This includes medical devices already on the market that are being evaluated for new intended uses, new populations, new materials or design changes.

**Investigational Medicinal Product (IMP)**

A pharmaceutical form of an active ingredient or placebo being tested or used as a reference in a clinical trial, including a product with a marketing authorization when used or assembled (formulated or packaged) in a way different from the approved form, or when used for an unapproved indication, or when used to gain further information about an approved use.

**Investigator / Principal Investigator**

An individual responsible for the conduct of a clinical trial at a trial site and ensures that it complies with GCP guidelines. If a trial is conducted by a team of individuals at a 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's Brochure (IB)**

A compilation of the clinical and nonclinical data on the investigational product(s) which is relevant to the study of the investigational product(s) in human participants. ICH GCP (R2) Section 7.3 outlines the content for a sufficient IB.

### Melbourne Children's Campus

MCRI is co-located with campus partners The Royal Children's Hospital and the University of Melbourne. Together the campus partners are known as the Melbourne Children's. On Campus, The Royal Children's Hospital is the custodian of clinical care, The Murdoch Children's Research Institute is the custodian of research and the University of Melbourne is the custodian of education.

### Participant Shadow File

Individual participant folder labelled with the name of the study in a consistent format with the main site file, and should contain:

- Signed Informed Consent Form (photocopy or original)
- Test results to confirm eligibility, if applicable.
- Documentation from study centre showing patient has been randomised (if applicable)
- File Notes related to the participant, e.g. protocol deviations
- Photocopy of letter to GP (if applicable)

### Product Information (PI)

Product information is defined in s3 of the [Therapeutic Goods Act 1989](#) to mean: 'in relation to therapeutic goods, information relating to the safe and effective use of the goods, including information regarding the usefulness and limitations of the goods'. The information in a product information document has been written by the pharmaceutical company responsible for the medicine and has been approved by the TGA.

A PI should contain the following information: Name of the medicine, Description, Pharmacology, Clinical trials, Indications, Contraindications, Precautions, Adverse effects, Dosage and administration, Overdosage, Presentation and Storage Conditions, Name and address of the sponsor, Poison schedule of the medicine, Date of approval.

### Protocol deviation

Accidental or unintentional changes to, or non-compliance with the research protocol that may/may not increase risk or decrease benefit or; does not have a significant effect on the participant's rights, safety or welfare; and/or on the integrity of the data. Deviations may result from the action of the participant, researcher, or research staff. A deviation may be due to the research participant's non-adherence, or an unintentional change to or non-compliance with the research protocol on the part of a researcher. Also refer to definition of serious breach. Examples of a deviation include:

- A rescheduled study visit
- Failure to collect a blood sample
- Participant's refusal to complete scheduled research activities.

### Recruitment status

Indicates the current stage of a clinical study and whether it is or will be open for enrolment.

|                |                        |   |
|----------------|------------------------|---|
| Open Studies   | Recruiting             | The study is currently recruiting participants.   |
|                | Not yet recruiting     | The study has not started recruiting participants.  |
| Closed Studies | Active, not recruiting | The study is ongoing (that is, participants are receiving an intervention or being examined), but potential participants are not currently being recruited or enrolled. |

|  |            |  |
|--|------------|--|
|  | Completed  | The study has ended normally, and participants are no longer being examined or treated (that is, the "last participant, last visit" has occurred). |
|  | Terminated | The study has stopped recruiting or enrolling participants early and will not start again. Participants are no longer being examined or treated.   |
|  | Suspended  | The study has stopped recruiting or enrolling participants early but may start again.  |
|  | Withdrawn  | The study stopped early, before enrolling its first participant.   |

### **Serious AE (SAE) / Serious ADR (SADR)**

AN SAE/SADR/SADE is any event/reaction that at any dose:

- Results in death
- Is life-threatening
- Requires inpatient hospitalisation or prolongation of existing hospitalisation
- Results in persistent or significant disability/incapacity, or
- Is a congenital anomaly/birth defect

### **Serious Adverse Event (device trials definition)**

An adverse event that:

- Led to death
- Led to serious deterioration in the health of the participant, that either resulted in:
  - A life-threatening illness or injury, or
  - A permanent impairment of a body structure or a body function, or
  - In-patient or prolonged hospitalisation, or
  - Medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function.
- Led to fetal distress, fetal death or a congenital abnormality or birth defect

### **Serious Breach (also known as protocol violation)**

A subset of deviation that is likely to affect to a significant degree: the safety or rights of a trial participant, or the reliability and robustness of the data generated in a clinical trial.

### **Significant Safety Issue (SSI)**

A safety issue that could adversely affect the safety of participants or materially impact on the continued ethical acceptability or conduct of the trial.

### **Sponsor**

An individual, company, institution, or organisation which takes responsibility for the initiation, management, and/or financing of a clinical trial.

### **Sponsor-Investigator**

An individual who both initiates and conducts, alone or with others, a clinical trial, and under whose immediate direction the investigational product is administered to, dispensed to, or used by a

participant. The term does not include any person other than an individual (e.g., it does not include a corporation or an agency). The obligations of a sponsor-investigator include both those of a sponsor and those of an investigator.

### **Suspected Unexpected Serious Adverse Reaction (SUSAR)**

An adverse reaction that is both serious and unexpected.

### **Source Data**

All information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents (original records or certified copies).

### **Source Document Verification**

The process by which data within the CRF or other data collection systems are compared to the original source of information (and vice versa).

### **Standard Operating Procedures (SOPs)**

Detailed, written instructions to achieve uniformity of the performance of a specific function.

### **Study Coordinator**

A research worker who works at a clinical research site under the immediate direction of a Principal Investigator, whose research activities are conducted under Good Clinical Practice guidelines. May also be called “Clinical Trial Coordinator” or “Research Coordinator”.

### **Sub / Associate investigator**

Any individual member of the clinical trial team designated and supervised by the Principal Investigator at a trial site to perform trial-related procedures and/or to make important trial-related decisions (e.g., associates, residents, research fellows, Study Coordinators). The PI will designate who will be nominated as Associate Investigators for that site.

### **Temperature Excursion**

A deviation in temperature from outside the approved temperature range for storage of a medicine. If there is an excursion from the approved storage conditions, the quality of the product may become unacceptable, and therefore the product may not be suitable for supply.

### **Trial Master File (TMF) / TMF Site Information File / Investigator Site File (ISF)**

The TMF contains all the essential trial specific documentation prepared/collected before the trial commences, during the conduct of the trial and at trial completion in accordance with Good Clinical Practice. The responsibility to hold and maintain an up to date TMF, including all superseded documents, is with the CPI.

The TMF Site Information File contains essential documents relating to a participating site in a multi-centre study. It is a **sub-section of the TMF**.

An Investigator Site File (ISF), sometimes referred to as the “study binder”, contains essential documents on the trial and forms/documents used by the individual site. The responsibility to hold and maintain an up-to-date ISF, including all superseded documents, is with the PI.

### **Unanticipated Serious Adverse Device Effect (USADE)**

Serious adverse device effect which by its nature, incidence, severity or outcome has not been identified in the current version of the risk analysis report.

### **Urgent Safety Measure (USM)**

A measure required to be taken in order to eliminate an immediate hazard to a participant's health or safety.

## **5. ASSOCIATED DOCUMENTS**

The following documents are available on the CRDO website at

[https://www.mcrc.edu.au/research/training-and-resources/clinical-research-development-office-crdo/resources-quantitative:](https://www.mcrc.edu.au/research/training-and-resources/clinical-research-development-office-crdo/resources-quantitative)

- CRDO guidance document and template, "Source document plan guidance and template"
- CRDO guidance document, "STUDY BINDERS - Guidelines, table of contents and section detail"
- CRDO guidance document, "PARTICIPATING SITE STUDY BINDERS – Instructions for Coordinating Lead Sites"
- CRDO Standard Operating Procedure, "Clinical Trial Registration of Investigator-Initiated Trials (IITs)".
- CRDO template, "Checklist for study initiation".
- CRDO template, "Clinical Monitoring Plan".
- CRDO template, "New SOP Template Wording".

The following documents are available from CRDO upon request:

- CRDO template, "Monitoring Visit Report".
- CRDO template, "TMF/ISF Checklist".
- CRDO template, "Plan for Unblinded Monitoring of Investigational Product - a Template for Investigator-Initiated Trials".

The following documents are not yet available but will be in the near future. Please contact CRDO for an update if you require the following:

- CRDO template, "Remote Monitoring Report".

## **6. REFERENCES**

ICH Topic E3 Note for Guidance on Structure and Content of Clinical Study Reports, (CPMP/ICH/137/95),

[http://www.ema.europa.eu/docs/en\\_GB/document\\_library/Scientific\\_guideline/2009/09/WC500002832.pdf](http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500002832.pdf)

ICH Topic E6 (R2) Integrated addendum to ICH E6 (R1): Guideline for good clinical practice (ICH E6 R2) with TGA annotations. Available from: <https://www.tga.gov.au/publication/note-guidance-good-clinical-practice>

NHMRC: Reporting of serious breaches of good clinical practice (GCP) or the protocol for trials involving therapeutic goods, EH59A), 2018. Available at: <https://www.nhmrc.gov.au/guidelines-publications/eh59>

NHMRC: Risk-based management and monitoring of clinical trials involving therapeutic goods, EH59B, 2018. Available at: <https://www.nhmrc.gov.au/guidelines-publications/eh59>

NHMRC: Safety monitoring and reporting in clinical trials involving therapeutic goods, EH59, Nov 2016. Available at: <https://www.nhmrc.gov.au/guidelines-publications/eh59>

Note for guidance on clinical safety data management: Definitions and standards for expedited reporting. (CPMP/ICH/377/95) annotated with TGA comments, DSEB, July 2000, <https://www.tga.gov.au/publication/note-guidance-clinical-safety-data-management-definitions-and-standards-expedited-reporting>

**DOCUMENT END**