Standard Operating Procedure

Title: **Trial Close Out for MCRI-Sponsored Investigator-Initiated Trials**

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1. PURPOSE

The purpose of this document is to describe the procedures related to the close-out of an MCRI sponsored investigator initiated clinical trial, both at a site level and at a study level, to ensure all required actions are completed prior to final analysis.

All MCRI sponsored investigator initiated clinical trials must be closed out in accordance with this Standard Operating Procedure (SOP).

1.1. Quality Improvement

Close-out is integral to the quality assurance of a clinical trial and GCP compliance of the study according to Sponsor requirements and to ensure that all necessary documents are in place should it be necessary for the trial information to be retrieved or inspected in the future.

2. BACKGROUND

Close-out and study closure refers to the process of ensuring that all study-related activities have been appropriately reconciled and that all relevant parties (review bodies, oversight committees etc.) have been notified.

Study Close-Out is designed to ensure that all necessary documents are within the Trial Master File (TMF) and the Investigator Site File (SF) and are ready for archiving and is defined as the act of ensuring that all clinical trial related activities are appropriately reconciled, recorded and reported at the end of a trial in accordance with the protocol, SOPs, GCP, and the applicable regulatory requirement(s).

A study may be closed for a variety of reasons. These include:

- When the study end point as defined in the trial protocol is reached
- Early closure because of safety issues
- Early closure because new information makes it clear that the question the study is
- designed to answer can be answered without further recruitment
- Early closure for any other reason, for example due to recruitment targets not being met or funder decision.

A COV typically occurs once the sponsor's recruitment target has been reached or sufficient positive or negative data results have been collected.

Site close out Visit's (COV's) consist of multiple activities that are performed to confirm that the site's obligations to the sponsor have been met and any post study obligations are understood as well as followed through. Closeout activities ensure that study procedures, all regulatory

documents and data are 100% completed, and any Investigational Medical Product (IP) or other trial supplies are returned or destroyed with documentation of the details pertaining to the destruction.

As per ICH-GCP E6 (R2) guidelines, sites require a close out monitoring visit to ensure that:

i. All trial documentation is appropriately completed prior to archiving
ii. All data is clean and complete with all queries being corrected and resolved, as well as trial data signed-off by the Principal Investigator (PI)
iii. All trial safety reporting (AEs/SAEs/SUSARs/SSIs/USMs) has been completed in accordance with the study protocol prior to site closure
iv. All serious AEs and SAEs reported have been resolved and/or followed up, as specified in the protocol
v. All Investigational Medicinal Products (IMPs) or Investigational Medical Devices (IMDs) are reconciled
vi. All biological samples have been received by the Central Lab and none remain at the site, if applicable
vii. All Regulatory documents are to complete and up to date with the originals maintained in the designated Investigator Site File (ISF) as agreed upon at study start up

As per ICH-GCP E6 (R2) guidelines, study-level close out activities are required to ensure that:

i. The Trial Master File (TMF) is complete and up to date and all necessary documents are located in the appropriate files
ii. All end of trial notifications have been completed and lodged
iii. All data has been cleaned, no data queries remain outstanding, and the trial database can be locked for final analysis
iv. All safety events have been reconciled as per protocol
v. All biological samples have been received by the Central Lab, if applicable
vi. All site payments are fulfilled.

3. SCOPE

This SOP applies to close-out activities conducted both at a site level and at a study level for MCRI sponsored investigator-initiated clinical trials.

This SOP provides the procedures for closing out participating trial sites along with the procedures for closing out the entire trial.

This SOP does not cover the procedures for the following:

- Close-out activities of externally sponsored clinical trials; either external commercially sponsored, investigator-initiated or collaborative group trials
- Archiving of the Trial Master File (TMF) and Site Information Files (SIFs) for MCRI-sponsored trials. This procedure is currently under development. Please contact the Clinical Research Development Office (CRDO) for further information.
- Archiving of Investigator Site Files (ISFs). Please refer to the MCTC170 | SOP Archiving of Clinical Trial Investigator Site Files.

4. RESPONSIBILITY

This SOP applies to all staff involved in conducting and managing MCRI-sponsored investigator-initiated trials (IITs) at MCRI: Sponsor-Investigators, Associate/Sub-Investigator(s), Clinical Trial Managers (CTMs), Clinical Trial Coordinators, research coordinators, trial monitors and other staff involved in research duties.

All staff are directly responsible for implementing the procedures set out in this SOP. This includes Clinical Trials involving Investigational Medicinal Products (IMPs), Investigational Medical Device (IMD) Trials, and other interventional studies.

The Clinical Trial Manager/Trial Monitor, or delegate, is responsible for conducting the COV, including reporting any follow up actions and notifying all of study closure and / or Temporary Halts.

The Clinical Trial Manager/Trial Monitor, or delegate, is responsible for ensuring all site level close out checks are completed, in accordance with the Site-Level Close Out Checklist (MCTC039) and confirming that all site level close out actions are followed up to resolution.

The Sponsor-Investigator or delegate is responsible for ensuring all study level close out checks are completed in accordance with the Study-Level Close Out Checklist (MCTC039) and confirming that all study-level close out actions are followed up to resolution.

A final close out of a trial can only be completed when the Sponsor-Investigator, or delegate, has reviewed both Participating Trial Sites and Sponsor files and confirmed that all necessary documents are in the appropriate files.

5. PROCEDURE

Close-Out Visits (COV) will be conducted at all participating trial sites once all participants have completed the study (including long-term follow-up visits if applicable), and the Coordinating Lead site has provided all required documents for inclusion in the ISF to the participating trial site.

There are a number of actions to be performed as part of the trial close out and these may vary according to the type of trial and the requirements of the Sponsor and Funder. The Sponsor-Investigator and members of the Central Trial Coordinating Team are responsible for identifying the specific actions for their trial.

Depending on the study, COV may be completed via:

i. Remote visit
ii. On-site visit

The Clinical Trial Manager/Monitor should prepare a Site Close-Out Visit Confirmation Letter (MCTC209) which includes the agenda covering the main end of trial actions and close-out visit procedures that will be undertaken (see Section 5.2 below).

5.1. When to Close-Out Sites

End of Study is typically defined as the last date in which it is expected that data is to be collected. The trial end date should be defined in the latest version of the trial protocol. If this is not specified in the protocol then the date of last patient, last visit (LPLV) should be used.

Site Closure activities may begin prior to end of study being declared, for example when a site's major activities have been completed (e.g. recruitment has finished but follow up still ongoing).

Confirmation of Site Closure should only be provided when all study related activities at that site are reconciled and/or complete.

A site will not be considered closed until data collection is complete and queries resolved where feasible (acknowledging that 100% data collection may not be achievable, however the expectation is that all data is required). All SAEs should have been followed up as per the study protocol and issues identified through monitoring activities are satisfactorily resolved.

The Central Trial Coordinating Team should organise a COV with the primary members of the Study Team no later than three months prior to the trial end date.

The primary members of the Central Trial Coordinating Team who should attend this meeting should include:

- Clinical Trial Manager/Trial Coordinator
- Sponsor-Investigator
- Trial Monitor (if applicable)
- Any other appropriate Central Trial Coordinating Team member e.g. Data Manager

It may be useful for other members of the Central Trial Coordinating Team (e.g. Data Manager and Research Nurse) to attend this meeting also and the Clinical Trial Manager/Trial Coordinator will be responsible for inviting them as required.

5.2. Premature Termination or Suspension of Trial

If the trial is prematurely terminated or suspended for any reason, the Sponsor- Investigator must:

5.2.1. Promptly inform the relevant parties of Sponsor, HREC, RGO, Regulatory Authorities (if applicable) and the TGA by providing a detailed written explanation of the premature termination or suspension.

5.2.2. Promptly inform the trial participants and their primary care physician where the trial participant has consented, of the termination or suspension and, if applicable, of the Investigational Product and dose they were administered.

5.2.3. Assure appropriate therapy and follow-up for the participant's continued care.

5.3. Site-Level Close Out Visit Preparation

The Clinical Trial Manager/Trial Monitor, or delegate, will confirm with the Site Principal Investigator (PI) and the site Study Team, the scope and format of the Close Out Visit (COV).

The Clinical Trial Manager/Trial Monitor, or delegate, will schedule a mutually beneficial time for the site COV to occur and determine whether the COV should be undertaken on-site or remotely.

The Clinical Trial Manager/Trial Monitor or delegate sends a Site Close-Out Visit Confirmation Letter (MCTC209) to the site confirming the time and format of the COV, outlining the activities that will be undertaken during the visit and detailing any preparation required by the site. This letter should be filed in the participating sites ISF.

Where required the Clinical Trial Manager/Trial Monitor, or delegate, will schedule time with any supporting departments (e.g. pharmacy, radiology, pathology) that participated in the trial to ensure their documentation is complete and that study materials and Investigational Medicinal Products (IMPs) / Investigational Agents / Medical Devices (IMDs) have been accounted for/reconciled.

The Clinical Trial Manager/Trial Monitor, or delegate, will review the most recent monitoring visit report and identify any outstanding actions to be resolved. These actions should be followed up with the Site PI for resolution during the COV, as appropriate.

The Clinical Trial Manager/Trial Monitor, or delegate, will prepare monitoring tools such as a blank Site-Level Close Out Visit Checklist (MCTC207) template and a Site-Level Close Out Follow-Up Letter (MCTC210).

5.4. Site-Level Close-Out Visit Activities

The Clinical Trial Manager/Trial Monitor or delegate will use the Site-Level Close Out Visit Checklist (MCTC207) to guide activities and ensure all site level close out activities are completed at the visit.

COV's can be conducted remotely (e.g. by telephone or video call) or onsite and in accordance with the trial's Clinical Monitoring Plan (CMP).

The following process should be followed when conducting a COV. The Clinical Trial Monitor or delegate should ensure the following items are discussed with the Site PI and the site study team during each COV; this list is not exhaustive and may vary according to the nature of the trial.

5.3.1. During the COV, the Site-Level Close Out Visit Checklist (MCTC207) and Site-Level Close Out Follow-Up Letter (MCTC210) will be used by the Clinical Trial Monitor, or delegate, as a guide to ensure that all site level close out activities are completed

5.3.2. Complete a full and final review of the ISF, according to the trial's CMP

5.3.3. Check that the End of Trial Notification has been submitted to the Local Research Governance Office (RGO), if applicable, and submission receipts filed in the relevant section of both the TMF/SIF and ISF

5.3.4. Check that all documents, including documents maintained by other departments, are filed appropriately, and file notes are present to provide explanation for missing documents. During trial conduct, if documents have been filed in other departments at the site, these documents must be reconciled and filed in the main ISF at site close-out in preparation for archiving

5.3.5. Confirm that all data queries have been resolved

5.3.6. Confirm that all source data and/or source documents have been filed appropriately

5.3.7. Complete a final Investigational Medicinal Product (IMP) accountability, including the return/destruction of IMP provided specifically for use in the trial, if applicable. This includes Pharmacy COVs and review of the Pharmacy Folder (PF), if maintained separately to the ISF.

5.3.8. Complete a final Investigational Medical Device (IMD) accountability, including the return/destruction of IMDs provided specifically for use in the trial, if applicable.

5.3.9. Confirm that all trial SAE Report Forms and Annual Safety Reports are complete and filed appropriately

5.3.10. Ensure arrangements have been made for any final sample shipments, if applicable. This includes liaising with the receiving site/central lab to ensure

they are able to accept the samples and arranging the shipment with a suitable courier service

5.3.11. Ensure any final invoices for site payments have been received from the participating trial site, if applicable

5.3.12. Ensure Site Principal Investigators are aware of their requirement to archive the ISF following the close out visit and provide the details of the archiving to the Trial Manager/Monitor or delegate (For trials recruiting at RCH/MCRI, refer to MCTC170 SOP | Archiving Clinical Trial Investigator Site Files)

5.3.13. Ensure you discuss the archiving process and responsibilities with the Site PI and/or members of the site study team. The outcome of the discussion must be documented in the Site-Level Close Out Visit Checklist (MCTC207) and also in a Site-Level Close Out Follow-Up Letter (MCTC210).

5.3.14. Conduct a de-brief meeting at the end of the COV with the Site PI and members of the site Study Team, to discuss any findings and any actions. If there are any serious issues uncovered at the COV, these must be raised with the Sponsor-Investigator and Site PI as soon as possible. If the Site PI is not available, then the COV follow-up discussion must be carried out via e-mail, summarising the findings of the COV.

5.3.15. Where a remote site COV cannot successfully verify all close out requirements have been completed, the Clinical Trial Manager/Trial Monitor, or delegate, must arrange a subsequent onsite close out visit.

5.5. Post Site Close Out Visit Activities

If there are missing documents noted during final ISF review, the Clinical Trial Manager/Trial Monitor or delegate will refer to the TMF/SIF or other relevant sources to locate required documentation. Documents can be provided to the Site PI with the final Site-Level Close Out Follow-Up Letter (MCTC210), detailing in the follow up letter the document(s) attached. Where essential documents are deemed absolutely unrecoverable, a file note can be used to detail attempts to locate the documents.

The following process should be followed:

5.5.1. After the visit, the Site-Level Close Out Follow-Up Letter (MCTC210) will be prepared by the Trial Monitor, or delegate, who conducted the visit. The letter should contain the findings and/or any actions identified during the COV.

5.5.2. A copy of the completed Site-Level Close Out Visit Checklist (MCTC207) must be sent to the Sponsor-Investigator for review and signing.

5.5.3. A copy of the completed Site-Level Close Out Visit Checklist (MCTC207) and Site-Level Close Out Follow-Up Letter (MCTC210) must be filed in the SIF.

5.5.4. Target times for completion of COVs, completion of documentation and disseminating follow up letters to Site PI should adhere to the timelines outlined in the trial's CMP. Where target times were not met, justification will be documented in the Site-Level Close Out Visit Checklist (MCTC207).

5.5.5. Any critical findings identified at a COV must be highlighted to the MCRI Sponsorship Committee as soon as possible, to be discussed at the next Sponsorship Meeting.

5.5.6. The Site-Level Close Out Visit Checklist (MCTC207) and Site-Level Close Out Follow-Up Letter (MCTC210) must be made available to the MCRI Sponsorship Committee if requested.

5.5.7. Actions identified during the COV will be followed up until resolution and in accordance with the trial's CMP.

5.5.8. Once all follow up actions have been addressed by the site and no further issues need resolution, the Trial Monitor, or delegate, will issue a Final Site-Level Close-Out Letter (MCTC211) to the site to confirm that close out for that site is complete and the ISF can be archived.

5.6. Study-Level Close-Out Preparation and Activities (Sponsor-Level)

When ready to close out the study, the Clinical Trial Manager/Trial Monitor or delegate will develop the Study-Level Close Out Checklist using the template Study-Level Close Out Checklist (MCTC039).

During the course of close out, The Clinical Trial Manager/Trial Monitor or delegate will use the Study-Level Close Out Checklist (MCTC039) to guide activities and ensure all study-level close out activities are completed at the visit. This Checklist can be used to track study-level close out progress.

During study-level close, the Clinical Trial Manager/Trial Monitor or delegate should complete the following activities; this list is not exhaustive and may vary according to the nature of the trial.

5.6.1. End of Trial Notification

There may be several different organisations who require a formal End of Trial Notification procedure to be followed when the trial ends. These will often require

notification from the Sponsor-Investigator; however, the Clinical Trial Manager will be responsible for ensuring these requirements are identified and discussed and coordinating the submission in a timely manner as required.

The main stakeholders who will need to be informed are listed below, however this is not an exhaustive list and will vary from trial to trial:

- MCRI Sponsorship Committee
- Therapeutic Goods Administration (TGA), if applicable
- Other international Regulatory Bodies as applicable e.g., FDA, MHRA, Health Canada
- Lead Human Research Ethics Committee (HREC)
- Other international Ethics Committee's/Institutional Review Boards (IRB), as applicable
- Participating Trial Site research teams
- Participating Trial Site Research Governance Office (RGO)
- Parties responsible for clinical trials systems and databases (e.g. MCRI REDCap Administrators, external EDC vendors etc)
- Parties responsible for the supply of Investigational Medicinal Product/s (IMP) and/or Investigational Medical Device/s (IMD)
- Clinical Trial Registries e.g. Clinicaltrials.gov, ANZCTR
- Trial Funding Body(s)
- Research/trial Participants (by way of lay summary of research findings/Final Letter to Participants; see Element 5: Communication of research findings or results to participants; of the National Statement)
- Trial Steering Committee (TSC) and/or Data Safety Monitoring Committee (DSMC) members, as applicable
- Vendors and/or sub-contractors (e.g. external Laboratories, service providers etc), as applicable

5.6.2. TMF QA Review

The Trial Monitor/Clinical Trial Manager will review the Trial Master File (TMF) for completeness as part of the study-level close out procedures.

The TMF QA SOP (MCTC084) and corresponding TMF QA Review Checklist (MCTC067) should be completed and filed within the TMF upon completion of the QA review.

The Trial Monitor (or delegate) should ensure that the TMF is up to date and complete.

This should include:

- Checking the TMF against the Table of Contents

- Liaising with relevant internal and/or external Teams (e.g. Statisticians and Data Management Team) to ensure that appropriate files have been added to the TMF
- Ensure the study specific TMF index is up to date including information of any missing or yet to be added files.

5.6.3. Data Cleaning

A final period of data reconciliation and cleaning should occur. The Clinical Trial Manager/Trial Coordinator should discuss this with the Data Manager for the trial and estimate how long this will take (based on current outstanding data, volume and type of queries).

However, a minimum of 6-8 weeks would usually be practical for this. The data should be cleaned and ready to be handed over to the Trial Statistician two weeks prior to the scheduled database lock date as this allows for any final queries or anomalies that may require resolution.

All participating trial sites will undergo a site COV, where appropriate, prior to final database lock. This will ensure any data related issues identified at site close out are resolved prior to analysis of the dataset. Any actions identified at COVs which impact the study dataset, pharmacovigilance (PV) or non-compliance line listings, must be resolved prior to final database lock. The Site-Level Close Out Visit Checklist (MCTC207) and Study-Level Close Out Checklist (MCTC039) highlight which actions require resolution prior to database lock.

Data cleaning should be undertaken in accordance with the trial's Data Validation Plan (DVP).

5.6.4. Revocation of Access to Study Systems

The Trial Monitor, in collaboration with the Data Manager, will ensure that all study specific IT systems (e.g. database, randomisation system, participant questionnaires, Participant Apps etc) are appropriately locked/closed, all required user permissions stripped, and user access revoked from all participating trial site personnel.

Revocation of access to study systems must occur once the sites close-out visit has been completed (where applicable), and all data cleaning activities and data related issues resolved.

5.6.5. Database Lock

The Data Manager and/or Trial Statistician should advise on a date for the database lock based on the length of time required to carry out the data analysis in relation to any reporting and publication deadlines and individual schedules.

Final database lock should only occur once all site close-out visits have been completed (where applicable), all data cleaning activities have been completed and all data related issues resolved.

5.6.5.1. Transfer of Site-Specific Datasets to Participating Trial Sites

All participating trial sites must receive a copy of their participants data (i.e. full clean dataset) in which they contributed to the trial once the database has been locked.

The MCRI Clinical Research Development Office (CRDO) can provide advice on the appropriate process for this (e.g. providing a data set via file transfer or arranging access to the database to allow the site to download the dataset) depending on the EDC system used.

The procedure of suppling participating trial sites with a copy of their complete trial dataset is currently under development. Please contact the Clinical Research Development Office (CRDO) for further information.

5.6.6. Final Data Safety Monitoring Committee (DSMC) and/or Trial Steering Committee (TSC)

Trial specific TSC and/or DSMC Charters should be followed along with the current protocol and any requirements from funding bodies, paying particular attention to the release of trial results and dissemination.

If a final TSC/DSMC Meeting at trial close-out is required as per the trial's TSC or DSMC charter, it will be the responsibility of the Clinical Trial Manager/Trial Coordinator to schedule any required meetings.

5.6.7. Dissemination of Trial Results (Authorship & Dissemination Plan)

The Trial Manager should facilitate discussion of the trial's Authorship and Dissemination Plan with the Sponsor-Investigator and Trial Steering Committee including establishing the authorship of the main paper and dissemination of research outputs. The process of dissemination of trial results to participants (i.e. Final Letter to Participants) should also be commenced as per the Authorship ad Dissemination Plan.

The MCRI Authorship Guideline sets out how authorship of preprints, peer review manuscripts, grants and other applicable research outputs should be managed by MCRI researchers.

5.6.8. Financial Close-Out

The Sponsor-Investigator/Clinical Trial Manager will be responsible for ensuring that all finances have been reconciled at the end of the trial and that the final grant acquittal has

been completed. The MCRI Grants Office will officially close the trial grant three months after the trial end date.

If any further expenses are expected after the grant closure, the Sponsor-Investigator/Clinical Trial Manager should confirm how much of the funds can be retained. All financial reporting will be compliant with the funding body's requirements and relevant MCRI policy and procedures. The Sponsor-Investigator/Clinical Trial Manager should remind MCRI Grants and MCRI Finance approximately 3 months before the financial reconciliation/final grant acquittal report is due, to ensure they have it scheduled.

5.6.9. Archiving

This procedure is currently under development. Please contact the Clinical Research Development Office (CRDO) for further information.

6. CORRECTIVE ACTIONS

Failure to follow this SOP may result in non-compliance with standards and regulations designed to generate high quality data and protect the safety of study participants, thereby resulting in poor quality data and/or harm to participants.

Any deviation from this SOP that results in a potential risk to the integrity of the data or safety of participants is to be investigated as per MCTC061 SOP Continuous improvement: A corrective and preventive action (CAPA) plan.

7. GLOSSARY

Central Trial Coordinating Centre

A group of MCRI researchers organised to coordinate the planning, development, operations and conduct of an MCRI-sponsored IIT, multi-centre, clinical trial.

Clinical Monitoring Plan (CMP)

In accordance with the Integrated Addendum to ICH E6 (R1) Guideline for Good Clinical Practice E6 (R2) Section 5.18.7 (that was formerly adopted by the TGA with annotations on 8 February 2018), the Sponsor should develop a monitoring plan that is tailored to the specific human subject protection and data integrity risks of the trial. This plan must describe the monitoring strategy, the monitoring responsibilities of all the parties involved, the various monitoring methods to be used, and the rationale for their use.

Clinical Research Development Office (CRDO)

CRDO provides education and training to facilitate and increase capacity for clinical and public health research across the Melbourne Children's campus. This includes the development and implementation of Standard Operating Procedures and templates to enable researchers to conduct high quality research.

Clinical Trial

The National Clinical Trials Governance Framework definition for a clinical trial is: any research study that prospectively assigns human participants or groups of humans to one or more health-related interventions to evaluate the effects on health outcomes. Clinical trials include but are not limited to:

- Surgical and medical treatments and procedures
- Experimental drugs and diagnostics
- Biological products
- Medical devices
- Health-related service changes
- Health-related preventative strategies
- Health-related educational interventions

The World Health Organization (WHO) definition for a clinical trial is: The definition of the term clinical trial for the purposes of this document is a clinical research study that:

- is interventional, with:
    - one or more intervention arms, pharmacological or nonpharmacological (including, but not limited to, medicines, cells and other biological products, surgical procedures, radiological procedures, devices, behavioural treatments, process-of-care changes and preventive care)
    - at least one control arm

- prospective assignment to intervention or control;
- aims to evaluate the effects of the intervention(s) on health-related outcomes;
- is carried out at any level of the health system, from community to intensive care settings

Corrective and Preventive Action Plan

A Corrective and Preventive Action (CAPA) plan is a quality system plan and incorporates:

1. Identifying the issue, including scope and impact
2. Identifying the root cause of the issue – how/why it occurred
3. Identifying actions to prevent recurrence of the issue (corrective action) or, identify actions to prevent an issue from occurring (preventive action)
4. Documenting that the corrective actions/preventive actions were completed
5. Documenting that the corrective/preventive action has resolved the problem

Critical Finding

A finding defined as one with the capacity to directly undermine the integrity of the entire study. It's a weakness of, or non-compliance with, one or more processes indicating a systematic quality assurance failure which, if not resolved, will cause harm to patients or data integrity and/or organisation reputation that requires the immediate notification and attention of senior management and clear timelines for resolution.

Critical finding examples include:

- Where evidence exists that the safety, wellbeing, rights or confidentiality of study participants has been (or has had significant potential to be) jeopardised.
- Where reason has been found to cast serious doubt upon the accuracy and/or credibility of study data.
- Where approval for the study has not been sought from one or more regulatory agency/body or granted from one or more regulatory agency/body (e.g. Ethics committee, Site governance) but the study has commenced regardless.
- Where significant procedures not covered/included on the consent form are being performed or where new procedures have been introduced into the study protocol but where participants who had consented prior to their introduction have not been asked to re-consent.
- Where following study approval, significant amendments have been made to the study protocol or documentation but no new request for approval has been submitted.
- Where inappropriate, insufficient or untimely corrective action has taken place regarding previously reported major findings.

Data Safety Monitoring Committee (DSMC)

An independent and multi-disciplinary group established by the trial sponsor to review, at intervals, accumulating trial data, in order to monitor the progress of a trial and to make recommendations on whether to continue, modify or stop the trial for safety or ethical reasons.

Early Termination

Defined as when study recruitment and follow-up are halted before the date set for completion. If the defined study end points have been achieved earlier than planned, this is not considered to be early termination.

End of Study

End of study means the last date in which it is expected that data is to be collected. For most clinical trials this will be the date of the last visit of the last participant. The study end date should always be stated in your study protocol.

End of Study Notification

The report required to be submitted to the appropriate oversight bodies when the end of a study is reached. May also be known as 'End of Trial Declaration'.

Essential Documents

Documents which individually and collectively permit evaluation of the conduct of a study and the quality of the data produced. These documents serve to demonstrate the compliance of the Investigator, Sponsor and monitor with the standards of Good Clinical Practice (GCP) and with all applicable regulatory requirements. Filing essential documents at the Sponsor site and participating trial sites also assists with the successful management of the trial.

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.

Human Research Ethics Committee (HREC)

A body which reviews research proposals involving human participants to ensure that they are ethically acceptable and in accordance with relevant standards and guidelines. The National Statement requires that all research proposals involving human participants be reviewed and approved by an HREC and sets out the requirements for the composition of an HREC.

International Conference on Harmonisation (ICH)

The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) is unique in bringing together the regulatory authorities and pharmaceutical industry to discuss scientific and technical aspects of drug registration.

Investigator

A person responsible for the conduct of the clinical trial at a trial site. There are four types of Investigator roles used to describe Investigators with different levels of responsibility for the conduct of clinical trials. These are described below.

Associate Investigator

Any individual member of the clinical trial team designated and supervised by the Principal investigator at a trial site to perform critical trial-related procedures and/or to make important trial-related decisions (e.g., associates, residents, research fellows). May also be referred to as sub-investigator.

Coordinating Principal Investigator (CPI)

If a study is conducted at more than one study site, the Principal Investigator taking the additional responsibility for coordination of the study across all sites in a region is known as the Coordinating Principal Investigator (CPI). This role applies to externally sponsored studies where the Sponsor may be a collaborative research group, commercial Sponsor or an institution. The Principal Investigator at each site will retain responsibility for the conduct of the study at their site.

Principal Investigator

The PI is the person responsible, individually or as a leader of the clinical trial team at a site, for the conduct of a clinical trial at that site. As such, the PI supports a culture of responsible clinical trial conduct in their health service organisation in their field of practice and, is responsible for adequately supervising his or her clinical trial team.

The PI must conduct the clinical trial in accordance with the approved clinical trial protocol and ensure adequate clinical cover is provided for the trial and ensure compliance with the trial protocol.

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.

Investigator-Initiated Trials (IITs)

A clinical trial which is initiated and organised by an Investigator i.e. an individual rather than a collaborative group, company, or organisation. In these cases, the Investigator will take on the role of the trial sponsor and will then be responsible for the extensive GCP and regulatory requirements associated with both the management and conduct of the trial.

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 authorisation 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.

Investigational Medical Device (IMD)

A device that is the subject of a clinical study designed to evaluate the effectiveness and/or safety of the device.

Investigator Site File (ISF)

Filing repository controlled by the site Principal Investigator. It is held at the trial site and contains all the essential documents necessary for the site trial team to conduct the trial as well as the essential documents that individually and collectively permit evaluation of the conduct of the trial at the site and the quality of the data produced.

Melbourne Children's

The campus encompassing all staff from The Royal Children's Hospital, Murdoch Children's Research Institute and Department of Paediatrics University of Melbourne who initiate or carry out research under one or more of these institutional affiliations.

Melbourne Children's Trials Centre (MCTC)

Melbourne Children's Trials Centre (MCTC) is a collaboration between the Royal Children's Hospital, The Murdoch Children's Research Institute, The Royal Children's Hospital Foundation and The University of Melbourne. This Centre brings together expertise in research, clinical practice, and education and incorporates anyone who initiates or carries out research under one or more of these institutional affiliations.

Monitor/Trial Monitor

A person appointed by the Sponsor to undertake the role of monitoring for the trial. Monitors should be appropriately trained and should have the scientific and/or clinical knowledge needed to monitor the trial adequately.

Murdoch Children's Research Institute (MCRI)

An Australian paediatric medical research institute located in Melbourne, Victoria, affiliated with the Royal Children's Hospital and the University of Melbourne. The institute has six research themes: cellular biology, clinical sciences, genetics, infection and immunity, population health, and data science.

Participant

A participant is a person that is the subject of the research.

Participant Information and Consent Form (PICF)

The PICF provides information about research and its requirements so that the prospective participant can decide if they wish to take part in the research. In general, this includes the purpose, methods, demands, risks, and benefits of the research. It must provide information to participants in a concise format that they are likely to understand. It must be participant centred.

Pharmacy Folder (PF)

The PF is the part of the ISF consisting of Essential Documents relating to pharmacy conduct at a specific site. The PF may be physically included in the ISF or may be a separate file, depending on the requirements of the study and the site. A PF will not be required for all studies or all sites depending on the level of involvement of the pharmacy.

Pharmacovigilance

Process of ongoing monitoring of the safety profile, combined with the ongoing assessment and evaluation of the risk-benefit of medicines. The process is important to identify adverse reactions/adverse device effects and changes in the known safety profile.

Protocol

A document that describes the objective(s), design, methodology, statistical considerations, and organization of a trial.

Quality Assurance (QA)

Covers all policies and systematic activities implemented within a quality system. QA ensures that data are recorded, analysed, and recoded in accordance with the protocol and GCP. The use of GCP guidelines ensures ethical and scientific quality standards for the design, conduct, recording, and reporting of HREC approved clinical trials that involve research participants.

Recruitment

Recruitment of participants for a research project (known as a study) is the process where people are identified and contacted for further discussion, provide informed consent, are screened and (where eligible) enrolled in a study.

Research Ethics and Governance Office (REG)

REG supports the HREC and institutional research governance processes at MCRI.

Research Governance Office (RGO)

The Office or coordinated function within Melbourne Children's which is responsible for assessing the site-specific aspects of research applications, make a recommendation to the CEO / delegate as to whether a research project should be granted authorisation at that site, and overseeing that authorised research at the site meets appropriate standards (research governance).

Royal Children's Hospital (RCH)

The Royal Children's Hospital is major specialist paediatric hospital in Victoria, the Royal Children's Hospital provides a full range of clinical services, tertiary care, as well as health promotion and prevention programs for children and young people. Its campus partners are the Murdoch Children's Research Institute and The University of Melbourne Department of Paediatrics, which are based on site at the hospital.

Source Data

Source data is the original recording of an item of data. "All information in original records and certified copies of original records or clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial." (Section 1.51, Notes for Guidance on Good Clinical Practice (CPMP/ICH/135/95) Annotated with TGA Comments).

Source Document

Source documents are documents which contain source data. When data is entered directly into your electronic Case Report Forms (data collection forms) or database, the Case Report Form/database becomes your source document for that information.

Sponsor

An individual, organisation or group taking on responsibility for securing the arrangements to initiate, manage and finance a study. For investigator-initiated trials, MCRI or RCH will act as the Sponsor but delegate many sponsor responsibilities to the Coordinating Principal Investigator. In this case the CPI has the role of both Sponsor and Investigator and hence the MCTC has adopted the term **Sponsor-Investigator** to reflect the dual role of the CPI in investigator-initiated trials.

Standard Operating Procedure (SOP)

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

Study Team

Refers to the extended group of people involved in a research study. This includes the investigator team and any additional members of staff who are involved in the set-up or conduct of the study e.g. research nurse, research assistants.

Temporary Halt

Refers to the stoppage of any study activity in any form which is not envisaged in the approved protocol and where there is intention to resume it.

Therapeutic Goods Administration (TGA)

The Therapeutic Goods Administration (TGA) is Australia's regulatory authority for therapeutic goods.

Trial Manager / Trial Coordinator

A Clinical Trial Manager / Trial Coordinator has a significant role in the management of the clinical trial at the Sponsor level and provides leadership in clinical trial activities to ensure that the trial is completed within budget, on time and of the highest quality. A Trial Coordinator is responsible for managing the planning, implementation, and tracking of the clinical monitoring process, administration, and start-up of the clinical trial at the participating site and maintaining an overview of the conduct of the trial at sites. Some common roles and responsibilities performed by the Trial Coordinator include:

- Participate in protocol development, CRF design and clinical study report writing
- Guide in the creation and development of important study documents and manuals
- Conduct feasibility assessments
- Develop study budgets
- Oversee participant recruitment
- Oversee overall trial conduct
- Ensure compliance of site-staff with the trials Standard Operating Procedures
- Ensures compliance to all regulatory requirements both at a local and international level
- Ensures compliance to all data protection requirements both at a local and international level
- Ensures compliance to all safety reporting requirements both at a local and international level
- Conduct team meetings and site-staff training programs
- Overall responsibility of the trial
- Supervise in-house clinical trial staff

Trial Master File (TMF)

Filing repository controlled by the Sponsor/Sponsor-Investigator. It is the collection of essential documents that allows the Sponsor responsibilities for the conduct of the clinical trial, the integrity of the trial data and the compliance of the trial with Good Clinical Practice (GCP) to be evaluated.

Trial Steering Committee (TSC)

Most commonly used in commercial trials and large international non-commercial trials, a TSC is appointed by the sponsor to provide independent expert oversight for the trial. The TSC may include investigators, other experts not otherwise involved in the trial and, usually, representatives of the sponsor. Although blinded, the TSC acts as a body that takes responsibility for the scientific integrity of the protocol and the assessment of study quality and conduct.

8. REFERENCES

- Site Close-Out and Archiving | National Standard Operating Procedures for Clinical Trials, including Teletrials in Australia 2020
- Integrated addendum to ICH E6(R1): Guideline for Good Clinical Practice ICH E6(R2), annotated with TGA comments
- Australian Clinical Trial Handbook | Guidance on conducting clinical trials in Australia using 'unapproved' therapeutic goods; version 2.4, August 2021
- National Statement on Ethical Conduct in Human Research 2023
- RCH HREC Final Letter to Participants Guideline; November 2023
- Royal Children's Hospital Research Ethics and Governance (REG) website – Annual and Final Reports Guidance
- Medicines and Healthcare products Regulatory Agency (MHRA) website: https://www.gov.uk/guidance/clinical-trials-for-medicines-manage-yourauthorisation-report-safety-issues#end-of-trial

9. RELATED DOCUMENTS

- MCTC209 Template | Site Close-Out Visit Confirmation Letter
- MCTC207 Template | Site-Level Close Out Checklist
- MCTC210 Template | Site-Level Close Out Follow-Up Letter
- MCTC211 Template | Final Site-Level Close-Out Letter
- MCTC039 Template | Study-Level Close Out Checklist
- MCTC026 SOP | Clinical Trial Registration of Investigator-Initiated Trials (IITs)
- MCTC046 SOP | Monitoring Visit Activities for Clinical Trials of Investigational Products
- MCTC199 SOP | Internal Auditing
- MCTC170 SOP | Archiving Clinical Trial Investigator Site Files
- MCTC084 SOP | Trial Master File (TMF) Quality Assurance
- MCTC067 Form| Trial Master File (TMF) Quality Assurance Review Checklist

DOCUMENT END