Standard Operating Procedure

Title: **Sponsor-Investigator/CPI Responsibilities in MCRI-Sponsored Investigator-Initiated Trials**

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Author

NAME and TITLE: Laura Galletta, Melbourne Children's Trial Centre (MCTC)

The author is signing to confirm the technical content of this document

Signature: Signed Electronically by:
Laura Galletta - laura.galletta@mcri.edu.au
06-Apr-2023 @ 09:42 AM AEST Reason: Authorship

Institution/Department name: Melbourne Childrens

Reviewed and Approval

These signatures confirm the reviewers agree with the technical content of the document and that this document is approved for implementation at the Melbourne Children's.

NAME and TITLE: Andrew Davidson, Medical Director of MCTC

Signature: Signed Electronically by:
Andrew Davidson - Andrew.Davidson@rch.org.au
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CONTENTS

1. PURPOSE

Clinical trials should be managed and conducted in accordance with the approved protocol, sponsor Standard Operating Procedures (SOPs), Good Clinical Practice (GCP) and relevant jurisdictional regulations and guidelines.

The purpose of this document is to define Sponsor responsibilities in the conduct of single-site and multi-site MCRI-sponsored investigator-initiated trials.

For non-commercial trials, both investigator-initiated trials and collaborative group trials, MCRI assumes the role of the Sponsor, however, MCRI as Sponsor, delegates many of its sponsor responsibilities to the Sponsor-Investigator/Coordinating Principal Investigator (CPI).

This SOP defines the Sponsor responsibilities when delegated the roles and responsibilities of an MCRI-sponsored IIT, where the Sponsor-Investigator is acting in the capacity of sponsor.

1.1. Quality Improvement

This SOP safeguards the quality of clinical trials by ensuring that the Sponsor-Investigator/CPI is made clearly aware of their delegated responsibilities when they are acting in the capacity of the Sponsor, as required by GCP.

1.2. Participant Safety

This SOP ensures the safety of participants by ensuring that the Sponsor-Investigator/CPI is made aware of the oversight role they encompass, including safety oversight, when they are acting in the capacity of the Sponsor.

2. SCOPE

GCP defines the Sponsor of a trial as either an individual, organisation or group taking on responsibility for securing the arrangements to initiate, manage and finance a study. Each institution will have its own policy regarding the sponsorship role.

For MCRI-sponsored investigator-initiated trials, MCRI will assume the role of the Sponsor, however, MCRI delegates many sponsor responsibilities to the Sponsor-Investigator/CPI. In this case, the Sponsor-Investigator/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.

3. RESPONSIBILITY

This SOP applies to all staff involved in conducting trials MCRI-sponsored Investigator-Initiated clinical trials, where MCRI is acting as the Sponsor, however, delegates sponsor responsibilities

to the Sponsor-Investigator/CPI. All staff are directly responsible for implementing the procedures set out in this SOP within their study teams.

4. PROCEDURE

4.1. Sponsor Responsibilities

Where the Sponsor-Investigator/CPI is acting in the capacity of Sponsor, the following responsibilities are delegated:

4.1.1. Before Study Commencement, the Sponsor-Investigator/CPI is Responsible for:

- Ensuring that Quality Assurance and Quality Control systems are in place so that trials are conducted, and data is gathered and reported in compliance with GCP, the trial protocol, institutional approvals, and any Therapeutic Goods Administration (TGA) requirements. *ICH GCP 5.1.1 and ICH GCP5.6.3.*
- Securing agreement from all involved parties to ensure direct access to all trial related sites, source data/documents, and reports for the purpose of monitoring and auditing by the sponsor, and inspection by domestic and foreign regulatory authorities. *ICH GCP 5.1.2.*
- Ensuring that no omissions occur which might disentitle themselves, the Hospital or HREC, to such indemnity as could otherwise be available under the Medical Indemnity and Public Liability Policies.
- Selection of the appropriate investigator(s) and institution(s) to conduct and complete the trial according to GCP standards. *ICH GCP 5.5.1.*
- Definitive, unambiguous allocation of trial-related duties and responsibilities to trial-related staff. *ICH GCP 5.7.*
- Ensuring provision of appropriate insurance and indemnity for the trial and trial related staff, as well as measures for participant compensation for trial-related injury. *ICH GCP 5.8.1 and ICH GCP 5.8.2.*
- Ensuring the confirmation of endorsement from the relevant HREC(s) / Governance Offices and notification of the approvals to the TGA. *ICH GCP 5.11.*
- Ensuring the trial is registered prior to first participant enrolled (with support from MCTC) on the applicable registries (i.e., clinical trials.gov (recommended) or ANZCTR).
- Ensuring that funding arrangements are declared in the Human Research Ethics Application (HREA) and Research Governance Office (RGO) applications.
- Trial design and appropriate analysis. *ICH GCP 5.4.*

- Data handling, record keeping, and overall trial management. *ICH GCP 5.5.*
- Ensuring that agreements made with the investigator/institution and any other parties involved with the clinical trial, are in writing. *ICH GCP 4.9.6 and 8.2.6.*
- Ensuring that there is clear definition as to the ownership of any Intellectual Property that may arise from the project.

4.1.2. Sponsor-Investigator/CPI Responsibilities during trial conduct

- Ongoing trial related risk identification and reporting to Sponsorship committee. *ICH GCP 5.0*.
- Ongoing management and oversight of trial activities designed to mitigate risk. *ICH GCP 5.0.6.*
- Operational management of support team working on the project, including project management of participating study teams located at other participating sites.
- Conducting systematic checks and actions during the trial to ensure trial success and completion (i.e., project and budget health checks)
- Ensuring medical expertise is on hand for trial-related medical queries or participant care. *ICH GCP 5.3 and ICH GCP 4.3.1.*
- Compliance with the trial design (per protocol) and assessment and management of protocol deviations. *ICH GCP 5.1.1.*
- Provision of adequate start-up and ongoing training of the protocol and trial related tasks for each study team member at all participating sites. *ICH GCP 5.0.4.*
- Ensure appropriate approvals are in place prior to conducting site initiation visits at all participating site (i.e., MCTC033 SOP | Regulatory green light approval process)
- Ensuring that Investigational Products are available to participants free of charge. *ICH GCP 5.14.1*.
- Taking appropriate urgent safety measures (with investigator) where necessary. *NHMRC Guidance: Safety Monitoring and Reporting in Clinical Trials Involving Therapeutic Goods 2016 ("The NHMRC Guideline").*
- Keeping records of all adverse events reported by investigators. *ICH GCP 5.18.4(m) (iii) and ("The NHMRC Guideline").*
- Ensuring appropriate manufacture, packaging, labelling/coding, and distribution to trial sites of all investigational medicinal products. *ICH GCP 5.13 and ("The NHMRC Guideline").*
- Ongoing safety evaluation and Adverse Event/Adverse Drug Reaction reporting. *ICH GCP 5.16.1 and ("The NHMRC Guideline").*

- Management of trial master file. *ICH GCP 8.1*
- Set-up Trial Master File/Site Investigator File for each participating site and ensure it is always audit ready. *ICH GCP 8.1*
- Management and safeguarding of participant data (the case report form), results and publications (maintaining participant anonymity, privacy, and consent) according to Australian and local jurisdiction data privacy legislation. *ICH GCP 2.11*.
- Management of 3rd party vendors and/or suppliers supporting the project. *ICH GCP 5.2.*
- Compliance with Monitoring/Audit/Inspection requirements. *ICH GCP 5.20.1.*
- Notification of any premature termination of the trial in question. *ICH GCP 4.12.2 and ICH GCP 5.21.*
- Completion of the Clinical Study Report, as required by the applicable regulatory requirement. *ICH GCP 5.22 and ICH GCP 8.4.8.*
- Archiving and retention of all records relating to the study for a period of at least 15 years from the end of the Trial (i.e., completion of data analysis) in the case of adults, and at least 25 years until the youngest participant had reached the age of 25. in the case of children. *Health Records Act 2001.*

4.1.3. For all MCRI-Sponsored IITs

As part of the MCRI Sponsorship Committee process [MCTC037b SOP | MCRI Sponsorship Committee Process for IITs], a Sponsorship Approval Certificate is issued once the Sponsorship Committee agrees to assume the role sponsor for the trial.

The Sponsorship Approval Certificate outlines the responsibilities allocated to the sponsor (MCRI) and the Sponsor-Investigator/CPI and forms the basis of the agreement of the delegation of sponsor responsibilities between MCRI and the Sponsor-Investigator/CPI.

When MCRI is acting as a local sponsor or is required to delegate sponsorship to another organisation, a Local sponsorship Agreement is entered into, along with the completion of a MCTC168 Roles & Responsibilities Matrix, and signatures are collected from representatives of each party. This process is covered in MCTC183 SOP | Delegation of Sponsor-Responsibilities in MCRI-Sponsored IITs.

5. GLOSSARY

Adverse Drug Reaction (AR)

Any untoward and unintended response to an investigational medicinal product related to any dose administered.

Adverse Event

Any untoward medical occurrence in a patient or clinical trial participant administered a medicinal product or other intervention. It does not necessarily have a causal relationship with this treatment.

Auditor

An independent person or organisation who performs a systematic and independent examination of research related activities and documents to determine whether trial related activities, documentation, and data management have been conducted according to the protocol, GCP and applicable regulatory requirements.

Case Report Form (CRF)

Data collection tool used to record all the protocol required information to be reported to the sponsor on each research/trial participant. The CRF may be paper or electronic.

Certified Copy

A copy (irrespective of the type of media used) of the original record that has been verified (i.e., by a dated signature or by generation through a validated process) to have the same information, including data that describe the context, content, and structure, as the original.

Clinical Trial

The World Health Organization (WHO) 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 Trial Research Agreement

An agreement between the Sponsor and a participating site that sets out the rights and obligations of each party in relation to the conduct of a clinical trial.

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.

Good Manufacturing Practice (GMP)

A set of principles and procedures that when followed helps ensure that therapeutic goods are of high quality.

A basic tenet of GMP is that:

- quality cannot be tested into a batch of product
- quality must be built into each batch of product during all stages of the manufacturing process.

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.

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.

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.

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 (PI)

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.

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

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.

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.

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.

Serious Adverse Event (SAE)

An adverse event is defined as serious if it:

- results in death
- is life-threatening
- requires hospitalisation or prolongation of existing hospitalisation
- results in persistent or significant disability or incapacity
- is a congenital anomaly or birth defect

Other important medical events will be considered an SAE when, based upon appropriate medical judgment, they may jeopardise the research participant safety and may require medical or surgical intervention to prevent one of the outcomes listed in the above definition. This can include diagnosis of cancer.

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.

Therapeutic Good

In relation to the evaluation, assessment and monitoring done by the TGA, therapeutic goods are broadly defined as products for use in humans in connection with:

- preventing, diagnosing, curing, or alleviating a disease, ailment, defect, or injury
- influencing inhibiting or modifying a physiological process
- testing the susceptibility of persons to a disease or ailment
- influencing, controlling, or preventing conception
- testing for pregnancy

This includes things that are:

- used as an ingredient or component in the manufacture of therapeutic goods
- used to replace or modify of parts of the anatomy

Therapeutic Goods Administration (TGA)

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

Trial Coordinator

A 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.

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.

6. REFERENCES

- The National Clinical Trials Governance Framework
- TGA Integrated Addendum to ICH E6 (R1): Guideline for Good Clinical Practice ICH E6 (2) 2016 – Annotated with TGA comments available at https://www.tga.gov.au/publication/note-guidance-good-clinical-practice
- Victorian Managed Insurance Authority Guidelines for Clinical Trials for Victorian Public Hospitals, July 2022
- TGA Guidance: Australian Clinical Trial Handbook: Guidance on conducting clinical trials in Australian using "unapproved" therapeutic goods, Version 2.2 October 2018, available at https://www.tga.gov.au/publication/australian-clinical-trial-handbook
- UK Policy Framework for Health and Social Care Research - Health Research Authority (hra.nhs.uk)

- NHMRC Guidance: Safety Monitoring and Reporting in Clinical Trials Involving Therapeutic Goods 2016

- Victorian Health Records Act 2001

7. COLLABORATORS

Name/Role	Department/Group	Affiliation
Kate Scarff / CRDO Lead	Clinical Research Development Office	MCRI
Iona Walton / Administrative Assistant	Melbourne Children's Trials Centre	MCRI

8. RELATED DOCUMENTS

MCTC065 | SOP: Start-Up Clinical Trials
MCTC056 | Checklist: Trial Development and Study Start-Up
MCTC037b | SOP: Sponsorship Committee Process for IITs
MCTC183 | SOP: Delegation of Sponsor Responsibilities in MCRI-Sponsored IITs

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