# Title: Standard Operating Procedure (SOP): Site Initiation for MCRI-Sponsored Clinical Trials

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|---|---|---|
| 1.0 | Laura Galletta | New issue |

## Contents

## ABBREVIATIONS

| | |
|---|---|
| CPI | Coordinating Principal Investigator |
| CRF | Case Report Forms |
| GCP | Good Clinical Practice |
| IIT | Investigator Initiated Trial |
| IP | Investigational Product |
| ISF | Investigator Site File |
| MCRI | Murdoch Children's Research Institute |
| MCTC | Melbourne Children's Trials Centre |
| PI | Principal Investigator |
| RGO | Research Governance Office |
| SI | Site Initiation |
| SIF | Site Information File |
| SIV | Site Initiation Visit |
| SOP | Standard Operating Procedure |
| TMF | Trial Master File |

## 1. PURPOSE

The purpose of this Standard Operating Procedure (SOP) is to describe the procedures to be carried out when initiating a new Participating Site (including RCH if they are a participating site) for a clinical trial sponsored by the Murdoch Children's Research Institute (MCRI).

The purpose of the site initiation (SI) is:

- To present the clinical trial to the participating site staff who will be involved
- To train them in the trial protocol
- To train them in trial-specific procedures prior to commencing the trial
- To ensure that the clinical trial is performed according to the protocol and all applicable local laws and regulations including Good Clinical Practice (GCP).

## 2. RESPONSIBILITY AND SCOPE

2.1. This SOP applies to all applicable persons responsible for the process of site initiation of MCRI sponsored investigator-initiated trials (IITs) at MCRI: Sponsor-Investigators/Coordinating Principal Investigators (CPIs), Principal Investigators (PIs), research coordinators and other staff involved in research duties.

2.2. All staff are directly responsible for implementing the procedures set out in this SOP when conducting MCRI-sponsored IITs. This includes clinical trials involving Investigational Medicinal Products (IMPs) (referred to as CTIMPs within the international clinical trial landscape), Investigational Medical Device (IMD) Trials, and interventional trials.

### 2.3. Sponsor-Investigator/CPI or delegate Responsibilities:

- Responsible for ensuring that the person(s) undertaking initiation is/are trained to carry out the clinical trial processes
- Responsible for providing clinical, medical and safety training and oversight

### 2.4. Person(s) undertaking Site Initiation (SI) (e.g. Trial Coordinator, members of the Central Trial Coordinating Team, or suitably trained person)

- Responsible for advising the participating site regarding the collation of essential documentation and providing training to site staff (as determined by the Sponsor-Investigator/CPI))
- Responsible for ensuring that all appropriate approvals are in place before the SI meeting is held and before recruitment commences
- Responsible for ensuring that the site staff are aware of their responsibilities and provide training where necessary
- Responsible for ensuring all SI documentation is completed post meeting and prior to commencement of the clinical trial at the participating site.

## 3. APPLICABILITY

This SOP is applicable to all MCRI-sponsored IITs conducted in Australian and/or international sites.

## 4. PROCEDURE

Prior to the start of recruitment at a new participating site, the Sponsor-Investigator/CPI or delegate must ensure that:

- The site has all relevant essential documentation and approvals as identified by Good Clinical Practice (GCP) and all applicable local laws and regulations in place; and
- That all key staff at the site who will be participating in the conduct of the clinical trial are appropriately trained and have the necessary skills and knowledge of the trial procedures.

### 4.1. Objective of the Site Initiation (SI)

**4.1.1.** The Site PI and site staff must be adequately trained in the protocol, Investigational Product (IP) (if applicable), safety, GCP, ethics and regulatory procedures prior to enrolling participants into a clinical trial.

**4.1.2.** All participating sites should have a SI performed in order to train and to confirm continued acceptability of the participating site to perform the clinical trial. All initiation activities must be documented.

### 4.2. Site Initiation and Process Flow

**4.2.1.** Site initiation must be completed prior to recruitment and prior to any study procedures that require informed consent. A site may be deemed "initiated" once:

a) Required approvals are in place for the site (i.e. Ethics approval, Research Governance Office (RGO) approval, Regulatory/Competent approvals
b) A fully executed site agreement is in place
c) The Site PI is familiar with the protocol requirements, relevant regulations/frameworks and roles and responsibilities
d) All essential documents & approvals are in place, as per MCTC033 SOP - Regulatory Green Light Approval for Clinical Trial Site Activation
e) The site has been provided with relevant documentation, equipment (including their ISF binder) and/or training to enable site staff to begin trial conduct and recruitment. Site staff training should be documented in the Investigator Site File (ISF) using the MCTC017 Template – Training Log
f) For a trial involving an Investigational Product (IP), the IP is available to the site, whether registered or unregistered product is being used, and adequately stored. IP must not be available to a particular site until approvals are in place for that site.

**4.2.2.** A SI meeting is necessary to complete the initiation process (see Section 4.6).

**4.2.3.** The following sequence of events describes the SI process flow:

a) Ethics and Regulatory submission and approval is obtained
b) Requesting of and collection of essential trial documents, as per MCTC140 Template – Essential Document Request Letter and MCTC033 SOP - Regulatory Green Light Approval for Clinical Trial Site Activation
c) Perform site initiation meeting

d) Site authorised to commence recruitment, as per MCTC033 SOP - Regulatory Green Light Approval for Clinical Trial Site Activation

e) Site officially activated to enrolment, as per MCTC016 Template – Notification of Site Activation.

**4.2.4.** Changes in sequence above are permitted under the following defined circumstances:

a) At the discretion of the Sponsor-Investigator/CPI or delegate, the SI may be performed prior to receipt of any of the following essential documents:

I. Ethics/Regulatory Approval or other country-specific regulatory approvals

II. Execution of the Site Agreement

III. Receipt of other essential documents as required within the MCTC034 Template – Regulatory Green Light Approval Form

- However neither supply of IP (if applicable) nor participant recruitment may commence until all essential documents are in place (as per MCTC033 SOP - Regulatory Green Light Approval for Clinical Trial Site Activation).
- The period between SI and the anticipated provision of the required outstanding essential documentation should ideally be no more than 15 working days. The decision of the Sponsor-Investigator/CPI or delegate should be documented and retained in the Trial Master File (TMF).

**4.2.5.** Refer to Appendix 1 for a flow diagram of the site initiation process.

## 4.3. Determining the Content of the Site Initiation (SI)

**4.3.1.** The Sponsor-Investigator/CPI and the Trial Coordinator will determine the content of the SI based:

a) Complexity of the trial protocol and clinical trial procedures
b) Other trial specific training plans, i.e. Investigators' Meeting
c) Issues identified at the site-feasibility stage, if applicable
d) Trial experience of site staff

**4.3.2.** The Sponsor-Investigator/CPI and the Trial Coordinator should produce a standard Master SI presentation (i.e. PowerPoint slide set) to assist with consistency of training across all participating sites. The SI presentation should include the following sections tailored to the protocol:

**Part 1: Protocol Review and Clinical Background**

- Clinical Background and Trail Hypothesis
- Aims and Objectives
- Trial Endpoints
- Study Design
- Study Schema
- Trial Intervention/Treatment
- Eligibility Criteria (Inclusion & Exclusion Criteria)

- Informed Consent Process
- Participant Randomisation/Registration Procedures
- Schedule of Activities / Trial Assessments
- Laboratory Sub-studies, if applicable
- Trial Specific Safety Reporting
- Trial Specific Training Material/Resources
- Participant Follow-Up Procedures
- Any Trial Specific Procedures

**Part 2: Trial Operations and Logistics**

- Site Staff and Facilities
- Site Staff Roles and Responsibilities
- Key Trial Documentation
- Screening Procedures
- Randomisation/Registration Process
- Pharmacy Requirements: IP supply, storage, and accountability
- Laboratory Sub-Studies Sample Collection, if applicable
- Unblinding Procedures, if applicable
- Source Documents & Record Keeping
- Source Data Verification Requirements
- How to Report AEs/SAEs/SUSARs/USMs/SSIs etc
- How to Report Protocol Deviation and Suspected Serious Breaches
- Trial Monitoring
- Closeout and Archiving
- Contact Details

**Part 3: Trial Database and Florence eBinders™ Training**

- Florence eBinders™ - eISF / Essential Documents
- Overview of the trial database/s
- CRF Completion Timeline / Guidelines
- Data Entry Procedures
- Source Documentation / Source Documents for Source Data Verification
- Recording AEs / SAEs
- Query Resolution Procedures
- Investigator Sign-Off on Data, if applicable

**4.3.3.** The Sponsor-Investigator/CPI and the Trial Coordinator will determine the length of the SI presentation and the SI participants. The Site PI must be present at the initiation meeting, and it is recommended that other key site staff are present so that specific trial issues can be addressed directly.

**4.3.4.** **For studies involving IMP only:** The level of involvement of pharmacy and the interactions between site and pharmacy during a Site Initiation visit will be variable from trial to trial and site to site. The Sponsor-Investigator/CPI and the Trial Coordinator (or delegate) must consider the requirements for pharmacy initiation. It may be appropriate to conduct a separate visit or provide separate remote initiation to the pharmacy.

## 4.4. Scheduling and Confirmation of Site Initiation (SI)

**4.4.1.** The Trial Coordinator will contact the participating site staff to arrange and agree on a mutual SI date and time, with respect to project timelines and other logistics, e.g. shipment of clinical trial supplies (as per Section 4.5 below)

**4.4.2.** The Trial Coordinator should provide written confirmation of the selected SI date, including the date, time and videoconference/in-person room details, to the Participating Site PI and key site staff, as per MCTC122 Template – Site Initiation Booking Letter

**4.4.3.** Along with the Site Initiation Booking Letter, a copy of the SI Agenda, as per MCTC132 Template – Site Initiation Agenda, should also be forwarded

**4.4.4.** Copies of both the Site Initiation Booking Letter and Site Initiation Agenda must be filed in the participating site's corresponding Site Investigator File (SIF), and ISF

**4.4.5.** The Trial Coordinator should ensure all necessary documents are prepared and available for the initiation meeting, including any documentation required as per MCTC033 SOP - Regulatory Green Light Approval for Clinical Trial Site Activation. Where the participating site is required to be initiated prior to first shipment of IP, all essential documents required according to Part A of the Green Light Form must have been reviewed and approved.

## 4.5. Delivery of Clinical Trial Supplies pre–Site Initiation

**4.5.1.** The Sponsor-Investigator/CPI or the Trial Coordinator should arrange for all trial supplies to be at the participating site for the SI including:

a) Investigational Product, if applicable. Note: mandatory essential documents must have been collected in advance in order to initiate IP supply/use at the site. Refer to MCTC033 SOP - Regulatory Green Light Approval for Clinical Trial Site Activation for initial drug supply shipment authorisation procedure
b) Case Report Forms (CRFs) if paper-based forms are being used
c) ISF Binder. If Florence eBinders™ is being used, then the Trial Coordinator must ensure that the participating site staff have completed the required mandatory training, prior to being granted access
d) Pharmacy Binder, if applicable
e) Laboratory kits for biological sub-studies
f) Additional trial-specific materials e.g. paper Randomisation Envelopes.

## 4.6. Performing the Site Initiation (SI)

### 4.6.1. Review of Trial Procedures and Training of Participating Sites

4.6.1.1. The Sponsor-Investigator/CPI or the Trial Coordinator should ensure that the participating site staff are familiar with the requirements of the protocol, trial intervention (if applicable), have been trained in all trial-specific procedures and the Site PI is made are aware of their GCP responsibilities

4.6.1.2. The Sponsor-Investigator/CPI and the Trial Coordinator should conduct the SI in line with the requirements set out in Section 4.3 above,

ensuring all aspects of the SI presentation slide set (i.e. PowerPoint presentation) have been delivered

4.6.1.3. All site attendees must sign the Site Initiation Attendance Log (MCTC136 Template – Site Initiation Attendance Log), to confirm they have received training

4.6.1.4. Copies of completed Site Initiation Attendance Logs must be filed in the participating sites corresponding SIF, as well as the participating sites ISF

4.6.1.5. The Sponsor-Investigator/CPI or the Trial Coordinator should also discuss with the participating site how site staff not present at the initiation meeting will be trained in the trial procedures and how this will be documented.

### 4.6.2. Investigational Product (IP)

4.6.2.1. If at the time of SI the IP has been delivered to the participating site or the site already has access to over-the-counter IP, the Trial Coordinator must ensure that the pharmacy (delegated to manage IP) is instructed that the IP can only be released/used once the site has been officially activated to commence recruitment

4.6.2.2. Refer to MCTC033 SOP - Regulatory Green Light Approval for Clinical Trial Site Activation for initial drug supply shipment authorisation procedure.

### 4.6.3. Key Participating Site Staff for Site Initiation (SI) Meetings

4.6.3.1. The site PI and key site staff, i.e. sub-Investigator(s), study coordinators/research nurses, pharmacy staff (for trials involving IP), data managers should be present at the SI

4.6.3.2. If the site PI cannot be in attendance, the SI should be re-scheduled to another time where the site PI can attend

4.6.3.3. It is not necessary to inform/invite hospital pathology when only routine blood tests are requested by the protocol.

## 4.7. Post Site Initiation (SI) Meeting Activities

### 4.7.1. Site Initiation (SI) Meeting Follow Up Report

4.7.1.1. Details of the SI meeting must be documented in a Site Initiation Follow Up Report (MCTC142 Template - Site Initiation Follow Up Report) within 7 working days of the meeting being held.

4.7.1.2. Any issues identified must be documented within the Site Initiation Follow Up Report and followed-up promptly with the participating site.

4.7.1.3. Completed reports must be filed in the participating sites corresponding SIF. Participating sites do not receive a copy of the completed Site Initiation Follow Up Report.

**4.7.2.** Site Initiation (SI) Follow Up Letter for Participating Sites

4.7.2.1. A Site Initiation Follow Up Letter (MCTC141 Template - Site Initiation Follow Up Letter) must be sent to the Site PI and other relevant site staff within 7 working days of the meeting being held.

4.7.2.2. The Site Initiation Follow Up Letter will confirm the activities performed at the meeting and include any actions the site must address in order to proceed to site activation.

4.7.2.3. A copy of the letter must be filed in the participating site's corresponding SIF and ISF.

**4.7.3. Collection of Documents Post Initiation Meeting**

Refer to Part B of the MCTC034 Template – Regulatory Green Light Approval Form for documents required post initiation meeting.

## 4.8. Notification of Site Activation

**4.8.1.** The site may be notified of Site Activation once all essential documents are in place and the MCTC034 Template – Regulatory Green Light Approval Form has been issued to confirm that the participating site is ready to commence recruitment.

**4.8.2.** A Notification of Site Activation Letter (MCTC016 Template – Notification of Site Activation) must be sent to the Site PI and relevant site staff to notify the site that they may commence recruitment/study procedures.

**4.8.3.** At this time, the Trial Coordinator must ensure the site has been granted access to the eCRF (i.e. database), any electronic randomisation system, and has received all required trial supplies in order to conduct the trial.

**4.8.4.** A copy of the Notification of Site Activation Letter must be filed in the participating site's corresponding SIF and ISF.

## 5. ASSOCIATED DOCUMENTS

- MCTC001 SOP – SOP Creation, Implementation and Revision
- MCTC056 Template – Checklist for Trial Development and Start-Up
- MCTC135 SOP – Establishing International Clinical Trials
- MCTC146 SOP – Regulatory Green Light Approval for Clinical Trial Site Activation
- MCTC034 Template – Regulatory Green Light Approval Form
- MCTC016 Template – Notification of Site Activation
- MCTC017 Template – Training Log
- MCTC025 Template – Signature & Delegation of Duties Log
- MCTC011 Guidance – Investigator Site File (ISF) Filing Guidance
- MCTC012 Guidance – Trial Master File (TMF) Filing Guidance
- MCTC013 Guidance – Site Information File (SIF) Filing Guidance
- MCTC014 Guidance - eTMF Filing Guidance Document for Investigator-Initiated Studies
- MCTC033 Guidance - eSIF Filing Guidance Document for Investigator-Initiated Studies
- MCTC071 Guidance - eISF Filing Guidance Document for Investigator-Initiated Studies
- MCTC140 Template – Essential Document Request Letter
- MCTC122 Template – Site Initiation Booking Letter
- MCTC132 Template – Site Initiation Agenda
- MCTC136 Template – Site Initiation Attendance Log
- MCTC142 Template - Site Initiation Follow Up Report
- MCTC141 Template - Site Initiation Follow Up Letter

Please email CRDO.info@mcri.edu.au if you have any issues in accessing these documents.

## 6. GLOSSARY

**Case Report Form (CRF)**
A paper or electronic data collection document used in human research. It is a tool used to collect data on each study participant. The CRF consists of CRF pages.

**Competent Authority**
A competent authority is any person or organisation that has the legally delegated or invested authority, capacity, or power to perform a designated function. Similarly, once an authority is delegated to perform a certain act, only the competent authority is entitled to take accounts therefrom and no one else.
The Europeans Medicines Agency (EMA) definition of Competent Authority is a medicines regulatory authority in the European Union.

**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 and have the role of Sponsor-Investigator (see definition below for further information).

**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.

**Essential Documents**
Documents which individually and collectively:

- Permit the evaluation of the conduct of clinical research and the quality of the data produced.
- Serve to demonstrate the compliance of the investigator, research team and sponsor with the standards of GCP and with all regulatory requirements.
- When filed appropriately and in a timely manner greatly assist in the successful management of clinical research by the investigator.
- Are usually audited or monitored by the sponsor and inspected by regulatory authorities as part of the process to confirm the validity of the clinical research conduct and data collection.
- Section 8 of ICH GCP guidance details the essential documents necessary for the conduct of clinical research.

**Ethics Committee (EC)**
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.

**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 subjects are protected.

**Investigational Medical Device (IMD)**
Medical device being assessed for safety or performance in a clinical investigation. Note: This

includes medical devices already on the market, that are being evaluated for new intended uses, new populations, new materials or design changes.

**Investigator/Principal Investigator/Coordinating Principal Investigator/Sponsor-Investigator**
An individual responsible for the conduct of a study, ensuring that the study complies with GCP guidelines. If a study is conducted by a team of individuals at a study site, the investigator is the responsible leader of the team and may be called the Principal Investigator (PI). In this instance they may delegate tasks to other team members. If a study is conducted at more than one study site, the Principal Investigator taking overall responsibility for the study and for the coordination across all sites is known as the Coordinating Principal Investigator (CPI). The Principal Investigator at each site will retain responsibility for the conduct of the study at their site. Where the PI or CPI takes on responsibilities of the Sponsor, this role is termed the Sponsor-Investigator.

**Investigator Site File (ISF)**
This file consists of essential documents related to that specific investigator site. This is kept at the investigator site.

**Melbourne Children's**
This term is used to encompass 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.

**Participating Site**
A hospital, health centre, surgery or other establishment or care facility at or from which a clinical trial is conducted. This may be more than one physical location and may be specified in the trial protocol.

**Research Governance Office**
Research governance is a framework for institutions to use to ensure research is conducted responsibly and safely and is scientifically and ethically sound. Research governance considers the legal compliance, financial management, accountability, and risk management associated with at a participating site.

**Site Agreement**
A written, dated, and signed agreement between the site and the Sponsor that sets out any arrangements on delegation and distribution of tasks and obligations and, if appropriate, on financial matters.

**Site Initiation**
Entails bringing the participating site team to the point where they can begin study related activities.

**Site Investigator File (SIF)**
This file consists of essential documents related to that specific investigator site in accordance with Good Clinical Practice. These files are maintained and kept by the Sponsor.

**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 (CPI). 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.

**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 within 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**
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.

## 7. APPENDIX 1 – PROCESS FLOW DIAGRAM