Title: Standard Operating Procedure (SOP): Study Start Up for Clinical Trials

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Document History

Revision	Modified by	Change No.	Description of Change
1.0	CRDO Natalie Rose	N/A	New Issue (2020)

Contents

1. PURPOSE

The purpose of this document is to describe the procedure for setting up any investigator-initiated clinical trial sponsored by MCRI or where MCRI is a participating site.

2. RESPONSIBILITY AND SCOPE

This SOP applies to all Melbourne Children's Campus staff who undertake the following roles associated with an MCRI-sponsored clinical trial:

- Sponsor-Investigator
- Principal Investigator (PI)
- All members of staff who manage, coordinate or advise on MCRI sponsored clinical trials

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

- Sponsor-Investigator – used when referring to Sponsor responsibilities
- Coordinating PI/ PI – used when referring to Investigator responsibilities at site level (multi- site and single-site clinical trials respectively).

<u>MCRI-led (MCRI-sponsored) IITs</u>

The responsibility for setting up trial sites is delegated to the CPI (for multi-site studies) or PI (for single-site studies). Alternatively, these activities may be delegated to a Clinical Research Organisation (CRO). This delegation will be agreed before the study begins and will be documented in the sponsorship/site agreements.

<u>IITs where MCRI is a participating site</u>

For externally-sponsored studies listing Melbourne Children's as a participating site, the external sponsor may have their own SOPs for study start up. In this circumstance, it is the

responsibility of the Melbourne Children's site PI to ensure that the external Sponsor's SOP(s) do not conflict with this SOP or any other MCRI SOPs/policies related to clinical research.

3. APPLICABILITY

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

4. PROCEDURE

4.1. Approvals

It is the responsibility of the PI to ensure that appropriate approvals are in place before the Site Initiation Visit (SIV) / Study Start-Up Meeting is held and before recruitment commences. All sites require ethical approval and governance authorisation but there are other processes that may apply and these are described below.

Clinical Trial Notifications (CTN) – for investigational drug / device trials only

Any medicine or device to be used in the clinical trial that is either (i) not registered on the Australian Register of Therapeutic Goods (ARTG) or (ii) is being used outside the conditions of its registration (i.e. as listed in the TGA approved Product Information) needs to be notified to the TGA to allow access to these unapproved goods under the CTN scheme. The scheme requires that the Sponsor lodges a notification and provides assurance that all the necessary parties have approved the study to start. The CTN is lodged with the Therapeutic Goods Administration (TGA) via the TGA's online portal. This includes Clinical Trial Exemption (CTX) approval.

At MCRI, the responsibility for CTN lodgement is delegated to the Melbourne Children's Trial Centre (MCTC) team. The MCTC team will lodge only after receiving evidence of ethics approval and governance authorisation for the site(s) listed in the notification. To request assistance with CTN preparation, the clinical trial PI/delegate should contact MCTC.

Trial Registration

The International Committee of Medical Journals Editors (ICMJE, including editors of the Medical Journal of Australia, Lancet, New England Journal of Medicine and others) has declared that they will not consider a trial for publication without evidence that it had been registered in a publicly accessible trials registry prior to enrolment of the first participant. The ICMJE has stated that submission of summary results to ClinicalTrials.gov will not be considered prior publication and will thus, not interfere with journal publication.

Trial registration must be completed via a registry that is either a primary register of the WHO International Clinical Trials Registry Platform (ICTRP) or ClinicalTrials.gov (which is a data provider to the WHO ICTRP). MCTC recommends registration with either ClinicalTrials.gov or Australian New Zealand Clinical Trials Registry (ANZCTR) but note that for any trial meeting the FDA Applicable Clinical Trials criteria ClinicalTrials.gov must be used (for details see the CRDO SOP Clinical Trial Registration of Investigator-Initiated Studies available on the CRDO website).

All MCRI-sponsored IITs should be registered before the first participant is enrolled (in order to be compliant with ICMJE and the Declaration of Helsinki). The process for registering trials takes some time. It is therefore recommended that the trial registration is submitted to the registry at least 21 days before the anticipated date of first participant enrolled.

4.2. Management of Essential Documents

(a) Trial Master File (TMF) [Sponsor responsibility]

The Sponsor-Investigator/delegate is responsible for setting up the TMF at the beginning of the clinical trial. It is recommended this activity is started as early as possible and at a minimum, during the protocol writing stage.

The TMF should be prepared according to the file structure outlined in Appendix 1 of the CRDO SOP *Management of Essential Documents*. For both paper-based and electronic TMF resources, please contact CRDO.

For multi-centre trials, the Sponsor-Investigator/delegate is responsible for setting up and maintaining a TMF Site Information File (SIF) for each site participating in the trial, before sites start recruitment. Please note that the TMF Site Information File is a subsection of the TMF and contains essential documents relating to an individual site. The SIF(s) should be prepared in accordance with the file structure outlined in Appendix 3 of the CRDO SOP *Management of Essential Documents*. The content includes documents that are specific to the site. Essential Documents that are common to all sites are filed in the TMF only (i.e. are not duplicated in the Site Information File(s)).

For single centre trials, solely carried out at Melbourne Children's, the TMF can be set up without the need of a separate Site Information File (SIF). In such cases, see Appendix 2 of the CRDO SOP *Management of Essential Documents* for a file structure outline. At the trial's completion, the TMF should be archived along with any other essential documents that were stored outside the TMF.

(b) Investigator Site File (ISF) [PI responsibility]

The Investigator Site File (ISF) is the storage place for essential documents that are managed/used by the Principal Investigator and research team at external participating sites. An ISF must be established for all research sites before recruitment begins. It is recommended that set-up is started as soon as the site has been selected.

The PI/delegate is responsible for setting up and maintaining the ISF and ensuring that all required documents are collected and filed in the ISF. Delegation of this task should be formally documented in the study delegation log.

The ISF should be prepared in accordance with the file structure outlined in the CRDO SOP *Management of Essential Documents*. Once established, the ISF should be kept in a secure location and be updated as the study progresses.

The Sponsor-Investigator/Delegate is responsible for providing new/amended trial documents to the Principal Investigator/delegate at each participating site for filing in the ISF. Please note that any data/documents shared with the Sponsor-Investigator or uploaded into a database/filing system that is managed by the Sponsor-Investigator should not contain identifiable participant data.

Although the responsibility for investigational product accountability rests with the Principal Investigator, it is usually delegated to an appropriately qualified person. For trials using the services of a Clinical Trials Pharmacy (strongly recommended for trials on campus), site pharmacy files should be stored within the site pharmacy department during the trial.

The TMF and ISF should be maintained in a ready state to allow for audit, inspection and /or monitoring on request, and that they are subsequently archived appropriately. That is, at the trial's

completion, the PI/Delegate at each site is responsible for archiving the ISF along with any essential documents that have been stored outside the ISF for the duration of the study (e.g. pharmacy records, participant shadow files). Archiving should be conducted in accordance to each site's local policy, unless alternative arrangements have been specified in either the protocol or clinical trial agreement.

4.3. Management of Investigational Drug/Device

Good clinical research practice requires that investigators and research teams ensure accurate accountability for any investigational drug or device used in a research project. Institutional responsibility requires that any investigational drug or device is used in the manner intended by the research project, is stored under appropriate controlled conditions, and is used only by (on) subjects who have consented to participate in the research project.

Although responsibility for Investigational Product (IP) management and accountability at the trial site rests with the Site Principal Investigator (PI), the PI may delegate responsibility for IP management to the site pharmacist or, where a pharmacist is not available or involved, to an appropriately qualified person.

The site pharmacist or the appropriately qualified person will undertake management of the Investigational Product at the Site. Where the delegation of this activity requires supervision (e.g. pharmacist or appropriately qualified person new to the role), the delegated activity is to be clearly documented on the supervision plan, the Delegation and Training Logs.

The investigator, pharmacist or appropriately qualified non-pharmacist, must:

- Ensure the Investigational Product is used only in accordance with the approved protocol.
- Maintain records of all aspects of the management of the investigational product. These records at a minimum should include: shipping documents; date of each transaction; quantities; batch/serial numbers; expiration dates/retest dates (if applicable); temperature logs showing the storage conditions of investigational product throughout the trial period; the set of unique code numbers assigned to the Investigational Product and to the trial participant; and record of destruction/return.
- Provide maintenance and calibration records for storage equipment (e.g. refrigerators, thermometers) in accordance with sponsor requirements
- Ensure that the Investigational Product is received, stored respecting correct temperature control, prepared, administered, shipped and destroyed as specified by the sponsor in accordance with the Protocol, pharmacy manual and applicable regulatory requirement. Consideration must be given to security of the Investigational Product, with restricted access to approved personnel.
- Ensure any deviation to required temperature, storage conditions, potential defect / issue with IP is notified to sponsor in a timely manner and in accordance with study Protocol. Follow study site quarantine process as applicable
- Explain the correct use of the investigational product to each participant and should check, at intervals appropriate for the trial, that each participant is following the instructions properly. Instruct participant where relevant to return empty and partially used medication containers at their next visit. Extra counselling by the investigator or delegate, for study participants regarding poor medication compliance may be required.
- Follow the trial's randomisation procedures, if any, and ensure, for blinded studies, the blind is broken only in accordance with the protocol. For a blinded study, the investigator must promptly document and explain to the sponsor any premature un-blinding (e.g., accidental un-blinding, un-blinding due to a serious adverse event) of the investigational product

- Where the investigational product is shipped to, or returned from, a satellite site, the appropriate transfer method, respecting temperature control and monitoring thereof, is to be used according to the sponsor's guidelines. Relevant documentation to accompany the shipment and filed accordingly at both sending and receiving sites.

4.4. Development of SOPs to Support the Conduct of a Study.

An SOP is a detailed, written instruction, the purpose of which is to achieve uniformity in the way a specific task or function is performed. Researchers involved in a clinical trial may identify the need for a new SOP, or a deficiency in an existing SOP. This signals the need to initiate the creation of a new SOP or revision of an existing SOP.

An SOP is a controlled document. It is created through a controlled documentation process, meaning that it cannot be modified without going through a documented process of approval. In order to maintain uniformity in the conduct of a clinical trial, SOPs relevant to each trial can be developed by following CRDO's SOP: Standard Operating Procedure (SOP) Creation, Implementation and Revision.

4.5. Training Staff: Site Initiation Visit / Start up Meeting; SOP Training

- Each site should have a pre-commencement meeting, known as either a Site Initiation Visit or a Start-Up Meeting. The meeting should be arranged for all research staff involved, including Pharmacy and supporting services as appropriate, once all the agreements and approvals are in place.
- At the meeting, the protocol should be reviewed with procedures highlighted and attention drawn to any study specific Standard Operating Procedures (SOPs). At the meeting, Participant Information and Consent Forms (PICFs) should also be reviewed. The clinical trial team should be reminded of the importance of research governance and adherence to the principles of) Good Clinical Practice (GCP, relevant legislation and subsequent amendments (if applicable).

The start-up meeting is also a good opportunity for the study staff to complete the delegation log and ensure their Curriculum Vitae (CV) is signed and on file.

4.6. "Green light" to Commence Recruitment

See CRDO's GUIDANCE Document: Recruitment, screening and enrolment of research participants, and CRDO's Checklist for Study Start-Up - Are you ready to start RECRUITING?

4.7. Other Study Start-Up Activities – not elsewhere included

- For all trials conducted at Melbourne Children's, the PI should hold evidence of TransCelerate-recognised GCP certification within the last 3 years. If individuals have not had training or it has expired, training must be attended prior to their involvement in the trial.
- The PI is responsible for ensuring that all members of the research team have received appropriate training on the study protocol and understand their role within the clinical trial.
- The PI should ensure that any tasks to be delegated are clearly documented on the delegation log and that trial team members and the PI sign the delegation log to indicate agreement with the delegation. In addition to signing the study delegation log, each member of the research team should be able to demonstrate that they are qualified by training and experience to perform their delegated tasks

- All information regarding study treatments (whether drug or non-drug) must be received prior to the start of the study (i.e. randomisation schedules and un-blinding, etc. (if applicable).
- The PI is responsible for ensuring that all supplies have been ordered and are available before recruitment begins. For example, all laboratory kits should be on site and the Case Report Form (CRF) should be available with relevant training and access organised for all staff.

5. GLOSSARY

Clinical Research Development Office (CRDO)
The Clinical Research Development Office (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.

Contract Research Organisation (CRO)
A contract research organisation (CRO) is a company that provides support to the pharmaceutical, biotechnology, and medical device industries in the form of research services outsourced on a contract basis. A CRO may provide such services as biopharmaceutical development, biologic assay development, commercialisation, preclinical research, clinical research, clinical trials management and pharmacovigilance.

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).

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.

Clinical Trial Notification (CTN) / Clinical Trial Exemption (CTX)
Clinical trials conducted using 'unapproved therapeutic goods' in Australia–that is, therapeutic goods that have not been evaluated by the Therapeutics Goods Administration (TGA) for quality, safety and efficacy and entered into the Australian Register of Therapeutic Goods (ARTG) for general marketing – are required to make use of the Clinical Trial Notification (CTN) or Clinical Trial Exemption (CTX) schemes. Under the CTN scheme, scientific and ethical review is provided by a human research ethics committee (HREC), with subsequent notification to the TGA. In the CTX scheme, the TGA has a direct role in the review of trial scientific data and must give an 'approval' for the proposed trial program to go ahead; however, HREC review is still required.

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.

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.

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.

Participant Information and Consent Form
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.

Research
"Includes at least investigation undertaken to gain knowledge and understanding or to train researchers" (National Statement on Ethical Conduct in Human Research 2007 [Updated May 2015]). For the purpose of this guidance, research includes any research that requires submission to and approval from an HREC and/or research governance office. This may include (but is not limited to) observational research, clinical trials, quality assurance projects and laboratory research.

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.

Standard Operating Procedure (SOP)
Detailed, written instructions to achieve uniformity of the performance of a specific function.

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

TMF 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.

6. REFERENCES

Note for guidance on Good Clinical Practice (CPMP/ICH/135/96) annotated with TGA comments DSEB, July 2000, sections 1 and 5

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