Title: Regulatory Green Light Approval for Clinical Trial Site Activation

Document ID: MCTC033
Version: 1.0

Author: Laura Galletta, Melbourne Children's Trial Centre (MCTC)

Author Signature:  **Date:** 2nd August 2021

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

Institution name: The Murdoch Children's Research Institute

Reviewed by: Kate Scarff, Melbourne Children's Trial Centre (MCTC)

Reviewer Signature:  **Date:** 30th August 2021

Reviewed by: Natalie Rose, Melbourne Children's Trial Centre (MCTC)

Reviewer Signature:  **Date:** 30th August 2021

These signatures confirm the reviewers agree with the technical content of the document and that this document is approved for implementation at the RCH Campus.

Approved by: Carolyn Stewart - Business Operations Manager, Melbourne Children's Trial Centre (MCTC)

Signature:  **Date:** 8 September 2021

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

Document History

Revision	Modified by	Change No.	Description of Change
1.0		N/A	New Issue

CONTENTS

1. ABBREVIATIONS

CA..... Competent Authority
CTA..... Clinical Trial Application
EEA..... European Economic Area
CPI.....Coordinating Principal Investigator
GCP .....Good Clinical Practice
GMP ..... Good Manufacturing Practice
ICH-GCP.....International Council of Harmonisation Good Clinical Practice
IIT ..... Investigator Initiated Trial
IMP.....Investigational Medicinal Product
IMPD .....IMP Dossier
IP ..... Investigational Product
LNR..... Low negligible risk
MIAIMP.....Manufacturer's Authorisation for Investigational Medicinal Product
MCRI .....Murdoch Children's Research Institute
MCTC ..... Melbourne Children's Trials Centre
MD ..... Medical Device
PSF .....Product Specification File
QP ..... Qualified Person
SIF ..... Site Investigator File
SOP..... Standard Operating Procedure
UK .....United Kingdom

2. 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 regulations.

The purpose of this SOP is to:

- describe the regulatory green light process for all investigator-initiated trials (IIT) where MCRI is acting as the Sponsor;
- ensure pre-trial activities and essential documentation requirements have been completed appropriately prior to permitting a participating site to commence enrolling into the trial;
- describe the approval process for the initial shipment of trial drug to a participating site;
- for international trials operating in the EU and UK, describe the processes for technical release or regulatory release of Investigational Medicinal Products (IMPs) by a Qualified Person (QP).

3. RESPONSIBILITY AND SCOPE

This SOP applies to all staff involved in conducting investigator initiated clinical trials at MCRI: Sponsor-Investigators/CPIs, PIs, Associate/Sub-Investigator(s), research coordinators and other staff involved in research duties.

All staff are directly responsible for implementing the procedures set out in this SOP within their research teams, when conducting MCRI-sponsored IITs, including Clinical Trials of Investigational Medicinal Products (CTIMPs), Medical Device (MD) trials and high-risk interventional trials. Observational studies (i.e. LNR) are considered low-risk studies and are not required to implement this SOP.

This SOP outlines the activities that must be undertaken and verified by the Sponsor (or delegate) and the Sponsor's notification to a participating site that trial recruitment activities can now commence.

4. BACKGROUND

Prior to authorising the start of a clinical trial and the initiation of participating sites, the sponsor must ensure that all approvals, contracts, and necessary essential documentation according to ICH-GCP (Section 8.2) are in place. Records must be available to verify that all necessary documents have been received by the sponsor prior to the authorisation to start the trial at each participating site. This should include confirmation that they have been reviewed by an appropriately delegated representative of the sponsor. Once this check is complete, the trial activities at the participating site can commence. This process is referred to as the 'regulatory green light' process.

5. PROCEDURE

The following sections provide a description of the processes to be followed when implementing this document's procedure.

5.1. Personnel Responsible

The Trial Coordinator (or delegate) will complete the appropriate checks and issue the 'green light' to individual sites by completion of the Regulatory Green Light Approval Form for each participating site. The Sponsor-Investigator/CPI will ensure that no participating site commences any research activity prior to receiving the sponsor's 'green light approval'.

5.2. Collation of Essential Document Package

The Trial Coordinator must ensure that all essential documentation as required by ICH-GCP (Section 8.2) are requested, reviewed and filed within the corresponding Site Investigator File (SIF) prior to the site initiation meeting being held. The essential documentation required prior to conducting the site initiation meeting are provided in Section 1A (Study-Level Items) and Section 1B (Site-Level Items) of the MCTC034_Regulatory Green Light Approval Form.

The additional essential documents required to authorise Investigational Product (IP) shipment (in addition to the documents in Section 1A and 1B) are listed in Section 3A of the Regulatory Green

Light Approval form. The Trial Coordinator must not authorise the supply of IP to a participating site until the sponsor has obtained all the required essential documentation.

All essential documentation must be reviewed for accuracy and currency and approved by the Trial Coordinator prior to populating the Regulatory Green Light Approval form.

Section 1A and Section 1B of the Green Light Approval Form must be reviewed and approved prior to conducting the site initiation meeting and prior to completing Section 2A. Where applicable, Section 3A can be completed in parallel to Section 1A/1B for drug trials. Section 2A cannot be executed alone.

5.3. Preparation of the Essential Documentation Package

The Trial Coordinator must populate the Regulatory Green Light Approval Form to record the essential documentation package for each participating site. Documents will be corrected as necessary by the Trial Coordinator (or delegate) until the package is complete. Copies of the essential documents collected must be filed within the corresponding SIF for each site.

5.4. Review of the Regulatory Green Light Approval Form

When the essential documentation package is complete (for either Section 1 or Section 2 (and/or 3), the Trial Coordinator must review the suite of essential documentation for accuracy and currency. Following review, the Trial Coordinator must sign Sections 1C, 2B and/or 3B, where applicable. Any issues requiring correction will be noted on the Regulatory Green Light Approval Form and followed up with the relevant participating site for amendment and/or correction by the relevant parties. The form must not be signed by the Trial Coordinator until all issues have been addressed.

When the review is completed and all required documentation is in place, the form will be signed by the Trial Coordinator. A signed Regulatory Green Light Approval Form will represent the green light to initiate recruitment activity at the participating site.

5.5. Execution of the Regulatory Green Light Approval Form

The essential documentation package has been successfully reviewed and approved when the Trial Coordinator has completed and signed the following sections:

1. Section 1C: Review of Essential Documents required prior to Site Initiation Meeting by Trial Coordinator
2. Section 2B: Review of Essential Documents required post Site Initiation by Trial Coordinator
3. Where applicable, Section 3B: Approval to Authorise Shipment of Investigational Product (IP) to Site/Site Activation.

5.5.1. Executing Section 1 of the Regulatory Green Light Form – Site Initiation

Section 1A and 1B of the Regulatory Green Light Approval Form must be completed, reviewed, and executed prior to conducting the site initiation meeting. Essential

documentation for the completion of Section 2 of the form are generally obtained following completion of the site initiation meeting.

5.5.2. Executing Section 2 of the Regulatory Green Light Form – Completion of Essential Documentation Collection

Upon completion of the site initiation meeting, Section 2 of the essential documentation package must be completed, reviewed, and executed prior to officially activating the participating site to recruitment. If there are any outstanding actions from the site initiation meeting, these must also be addressed and resolved by the participating site.

Note: If the trial involves an IP and is operating in the EU or UK, Section 3 of the Regulatory Green Light Form must also be completed prior to officially activating the participating site.

5.5.3. Executing Section 3 of the Regulatory Green Light Form – Approval to Release IMP – EU and UK Sites Only

Where applicable (i.e. for EU and UK participating sites only), Section 3 of the Regulatory Green Light Approval Form must be completed, reviewed, and executed prior to officially activating the participating site to recruitment. The participating site will be approved to commence recruitment when Section 1 and 2 of the Regulatory Green Light Approval Form have been executed and Section 3 has received final signature for Investigational Product (IP) to be released to the site. Refer to Section 4.6 below for further details on the two-step IMP release process within the EU and UK.

Note: The participating site must be approved to use the IP prior to commencement of recruitment (i.e. Section 1 and Section 2 satisfactorily completed), regardless of when the actual first drug release takes place (e.g. a trial where drug is supplied after site activation).

5.6. Two-Step IMP Release

The following section provide a description of the processes to be followed when documenting IMP release in the EU and UK.

Step One

The Qualified Person (QP) batch certification is the first of the two-step release process. This is applicable when a Manufacturers Authorisation for Investigational Medicinal Product (MIAIMP) is required, i.e., a manufacturer and/or importer is listed on the clinical trial application to a competent authority for certification of finished IMP or placebo.

Step Two

The regulatory green light is applicable to all trials involving an IMP. Further guidance should be sought from the Sponsor in cases where the IMP will be sent direct from the IMP supplier or manufacturer to the participant without the involvement of Pharmacy.

5.7. QP Batch Certification

- This is the certification by a QP, as defined in the regulations, before a finished IMP batch is released for use within a clinical trial, confirming that the requirements of Article 13(3) of Directive 2001/20/EC have been met.
- The QP has a legal responsibility as defined in Article 13(3) to ensure that the IMP has been manufactured in accordance with EU GMP and meets the conditions of the product specification files (PSF), IMP dossier (IMPD) and clinical trial authorisation (CTA).
- A prerequisite of QP batch certification is receipt of the full Clinical Trial Application, IMP, cannot be authorised for distribution prior to the CTA being granted.
- The QP certification must be provided by a QP named on the MIA(IMP) licence specified in the Clinical Trial Application as responsible for the manufacturing and/or importation of the finished IMP.
- The QP certification statement is the final release of the batch.
- Certification is issued for each batch produced and must be retained by the sponsor – or delegate for review by competent authorities until the end of the trial archiving period.
- Additionally to QP certification, if an IMP is manufactured outside the EEA or UK, a QP declaration of equivalence to EU GMP is required for each IMP that is listed in the Clinical Trial Application.
- For multicentre MCRI-sponsored IMP trials, it is the sponsor's responsibility to hold the QP certification documents, and to have a system to track IMP to site on a batch-specific basis to enable management of expired stock and recall if required. QP batch certificates may be supplied to other participating sites, either by design or upon request, unless this would compromise the blinding of a trial.

5.8. Regulatory Release and Authorisation to Start Recruitment

This is the second of the two-step process and is performed for each participating site. After the QP batch certification has occurred, the sponsor will then authorise the commencement of the clinical trial as long as the provisions of the EU clinical directive have been met. They are:

- Favourable opinion from the Ethics Committee
- Notice of Acceptance/Approval from the Competent Authority
- Favourable opinion from the Gene Therapy Advisory Committee, or equivalent (only applicable to clinical trials using somatic cell therapies)
- The Sponsor is legally responsible for ensuring the above steps are completed prior to the release of IMPs for use in a clinical trial
- The IMP should not be released for use to the participating sites before ethics committee or competent authority approvals are in place

- Any IMP received at the participating sites before the required approvals are in place should either be quarantined or returned to the supplier (at the discretion of the sponsor) until all the required approvals are obtained.

Where applicable, the Trial Coordinator must complete Section 3 of the Regulatory Green Light Approval Form, prior to release of IMP to site and officially activating the participating site to recruitment. The participating site will be approved to commence recruitment only when Section 1 and 2 of the Regulatory Green Light Approval Form have been executed and Section 3 has received final signature for study drug to be released to the site.

5.9. Filing of Documents

The Trial Coordinator must ensure that the fully executed Regulatory Green Light Approval Form, documents associated with the essential documentations package and any significant correspondence to and from the participating site are filed in the relevant sections of the corresponding SIF.

6. ASSOCIATED DOCUMENTS

- MCTC065 SOP – Study Start Up for Clinical Trials
- MCTC135 SOP – Establishing International Clinical Trials
- MCTC034 Template – Regulatory Green Light Approval Form
- MCTC012 Guidance – Trial Master File (TMF) Filing Guidance
- MCTC011 Guidance – Site Information File (SIF) Filing Guidance
- MCTC011 Guidance – Investigator Site File (ISF) Filing Guidance

For documents referenced within this SOP that are not currently available on the CRDO Launching Pad, please email CRDO.info@mcri.edu.au to obtain a status update.

7. GLOSSARY

Batch
A defined quantity of starting material, packaging material or product processed in one process or series of processes so that it could be expected to be homogeneous.

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 Application (CTA)
A Clinical Trials Application (CTA) is the application/submission to the competent National Regulatory Authority(ies) for authorisation to conduct a clinical trial in a specific country. Examples of submissions to competent National Regulatory Authorities may include but are not limited to:

1. Application/submission to a competent National Regulatory Authority within the European Union (EU) to request an authorisation concerning a clinical trial, as envisaged in Article 9, paragraph 2, of Directive 2001/20/EC

2. Investigational New Drug Application (IND) for any product filed with the U.S. Food and Drug Administration (FDA) pursuant to Title 21 of the Code of Federal Regulations, Part 312 (U.S. sites)

3. Any comparable application/submission to a National Regulatory Authority in another country or territory other than the U.S. or the EU, for example the Therapeutic Goods Administration (TGA) in Australia (i.e. the CTN/CTA application).

Clinical Trial Authorisation
Clinical Trial Authorisation means all approvals, licenses, registrations, or authorisations from the relevant Competent Authority necessary to conduct a human clinical trial on a Product in a country.

Examples of Clinical Trial Authorisations may include but are not limited to:

1. Within the UK, Clinical Trial Authorisation or “CTA” means a clinical trial authorisation filed with the Medicines & Healthcare Products Regulatory Agency (MHRA) as necessary to commence human clinical trials of a drug in conformance with applicable laws and regulations.

2. Within Australia, Clinical Trial Approval or “CTA” is one of two schemes used by the Therapeutic Goods Administration (TGA) to authorise the supply of unapproved therapeutic goods, including medicines, medical devices and biologicals, to participants participating in clinical trials in Australia. The CTA scheme is appropriate for trials where the approving ethics committee does not have access to the appropriate scientific and technical expertise to review the trial under the CTN scheme. It is generally used for high risk or novel treatments, such as gene therapy, where there is no or limited knowledge of safety.

Clinical Trial Notification (CTN)

One of two schemes used by the Therapeutic Goods Administration (TGA) to authorise the supply of unapproved therapeutic goods, including medicines, medical devices and biologicals, to participants

participating in clinical trials in Australia.

The CTN scheme is appropriate for trials where the approving ethics committee has enough scientific and technical expertise to review the proposed use of the unapproved therapeutic good(s). The majority of investigator-initiated trials would be in this category.

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.

Competent Authority (CA)
A competent authority is any person or organization 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 Principal Investigator (CPI)/Sponsor-Investigator
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). For MCRI sponsored Investigator-Initiated trials, where the CPI takes on responsibilities of the Sponsor, this role is termed the Sponsor-Investigator.

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 subjects are protected.

IMP Dossier (IMPD)
The IMP dossier (IMPD) gives information related to the quality of any IMP (i.e. including reference product and placebo), manufacture and control of the IMP, and data from non-clinical studies and from its clinical use. However, in many cases where the IMP has a marketing authorisation, an IMPD is not required.

Investigational Product (IP) / 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, a new patient group or when used to gain further information about an approved use.

Note: This definition includes biologicals used as investigational medicinal products.

Investigator
A person responsible for the conduct of the clinical trial at a trial site. There are three 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 (AI)
Any individual member of the clinical trial team designated and supervised by the 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.

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 / Coordinating Principal Investigator (CPI)
In investigator-initiated and collaborative research group trials, the Principal Investigator taking overall responsibility for the study and for the coordination across all sites (if it is a multi-centre trial) is known as the Sponsor-Investigator or Coordinating Principal Investigator (CPI). In this case, the Sponsor will delegate many sponsor responsibilities to the Sponsor-Investigator/Sponsor-Investigator.

Investigator-Initiated Trials (IITs)
Trials where the investigator initiates and organises a trial with minimal involvement of the institution are referred to as investigator-initiated trials (IITs). In this case, the institution will be usually be responsible for the medico-legal risk and delegate the remaining Sponsor responsibilities to the lead investigator (i.e. Sponsor-Investigator), including the initiation, financing (or arranging the financing) conduct and management (including compliance with GCP and applicable regulatory requirements) of the trial.

Melbourne Children's
Melbourne Children's is a collaboration between campus partners The Royal Children's Hospital (RCH), Murdoch Children's Research Institute (MCRI) and The University of Melbourne.

Melbourne Children's Trial Centre (MCTC)
MCTC is a unique 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 bring 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.

Product Specification File (PSF)
A reference file containing, or referring to files containing, all the information necessary to draft the detailed written instructions on processing, packaging, quality control testing, batch release and shipping of an investigational medicinal product.

Qualified Person (QP)
A Qualified Person (QP) is responsible for assuring the safety, quality and efficacy of the medicinal product, over its lifetime. QP is responsible of certifying batches of medicinal products before their use in clinical trials or available on the market, ensuring the performance of them. QPs know and understand all the possible factors that can affect the safety and the quality of medicines and supply chains.

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.

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 (TMF)
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.

8. REFERENCES

1. REGULATION (EU) No 536/2014 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of 16 April 2014 on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-1/reg_2014_536/reg_2014_536_en.pdf

2. ICH-GCP Integrated Addendum to ICH E6(R1): Guideline for Good Clinical Practice E6(R2)

   https://database.ich.org/sites/default/files/E6_R2_Addendum.pdf

3. Annex 13: EudraLex Volume 4: EudraLex - Volume 4: Good Manufacturing Practice: https://ec.europa.eu/health/documents/eudralex/vol-4_en

4. A 101 Guide to Qualified Person (QP) Release in Clinical Trial Supply: https://www.iqpc.com/media/8589/27354.pdf

DOCUMENT END