Title: Establishing International Clinical Trials

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Signature: ..... **Date: 12th August 2021**

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Document History

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

CONTENTS

ABBREVIATIONS

AE	Adverse Event
APP	Australian Privacy Principals
CA	Competent Authority
CMP	Clinical Monitoring Plan
CPI	Coordinating Principal Investigator
CRF	Case Report Form
CRO	Contract Research Organisation
CTIMP	Clinical Trials of Investigational Medicinal Product
CTRA	Clinical Trial Research Agreement
CTU	Clinical Trials Unit
DMP	Data Management Plan
DPIA	Data Protection Impact Assessment
DTA	Data Transfer Agreement
EC	Ethics Committee
ECRIN	European Clinical Research Infrastructure Network
EEA	European Economic Area
EMA	Europeans Medicines Agency
FDA	Food and Drug Administration
FDR	Food and Drug Regulations
FTE	Full Time Equivalent
GCP	Good Clinical Practice
HREC	Human Research Ethics Committee
IB	Investigator Brochure
ICH-GCP	International Council of Harmonisation of Good Clinical Practice
IIT	Investigator Initiated Trial
IMD	Investigational Medical Device
IMP	Investigational Medicinal Product
MCRI	Murdoch Children's Research Institute
MCTC	Melbourne Children's Trials Centre
MD	Medical Device
MHRA	Medicines and Healthcare products Regulatory Agency
MTA	Material Transfer Agreement
NCC	National Coordinating Centre
NIAID	National Institute of Allergy and Infectious Diseases
NZ	New Zealand
OHRP	Office of Human Research Protections OHRP
PI	Principal Investigator
PICFs	Patient Information & Consent Form
QMS	Quality Management System
QoL	Quality of Life
RCA	Research Collaborative Agreement
RCH	The Royal Children's Hospital
RL	Regional Lead
RSI	Reference Safety Information
SAE	Serious Adverse Event
SADE	Serious Adverse Device Effects
SAR	Serious Adverse Reactions
SOP	Standard Operating Procedure
SUSAR	Suspected Unexpected Serious Adverse Reactions
UK	United Kingdom
USM	Urgent Safety Measure
WHO	World Health Organisation

2. PURPOSE

The purpose of this Standard Operating Procedure (SOP) is to outline considerations for establishing, developing, and conducting MCRI-sponsored investigator-initiated clinical trials (IITs) that include participating sites outside of Australia, and to ensure that these studies are established and managed in accordance with MCRI, MCTC, Regulatory, Research Governance, ICH-GCP and country-specific requirements and local laws.

The document distinguishes between regulatory, legal, and good practice requirements, and indicates which aspects of these are relevant to wider clinical research. It includes an overview of trial practices and where required, more detailed information.

3. RESPONSIBILITY AND SCOPE

This SOP applies to all staff involved in developing and conducting MCRI-sponsored investigator-initiated trials (IITs) 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 when establishing MCRI-sponsored IITs with international participating sites. This includes Clinical Trials involving Investigational Medicinal Products (IMPs) (referred to as CTIMPs within the international clinical trial landscape), Investigational Medical Device (IMD) Trials, interventional and observational studies.

This SOP is applicable whether the involvement of international sites is known at the study conception/development phase, or whether an international site is added during study conduct.

4. BACKGROUND

The importance of conducting medical research on an international scale has many benefits. Globally, clinical trials are under increasing pressure to meet participant recruitment goals quickly and efficiently, and with very limited resources.

Developing and implementing international clinical trials is a complex endeavour with many additional factors that require consideration. By following this SOP and associated checklist, the MCRI Central Trial Coordinating Team can effectively navigate the challenges of international clinical trial start-up, potentially reducing the development time taken to establish an international clinical trial.

5. PROCESS

The following sections provide a description of the processes to be followed when implementing this SOP.

5.1. Funding

There are many additional costs in establishing an international clinical trial. Please consider these at the point of grant/funding application. As trial Sponsor, MCRI does not cover these costs, for example:

- **Regional Lead / In-Country Lead Site / National Coordinating Centre:** Consider whether a 'lead-site' should be selected for each country and contracted/delegated to perform additional tasks, e.g. streamline ethics submissions for the country. If so, this will usually include additional payments to support the contracted/delegated activities.
- **Ethics Committee (EC) and Competent Authority (CA) Reviews:** In some countries, these reviews require payment. Fees are considerably more than those charged by Australian Ethics Committees and the TGA.

- **Costs for Professional Translation Services:** Back-translation of any PICFs and/or other study documents from the foreign language into English.
- **Insurance Costs:** The insurance policies held by MCRI do not cover clinical trial activity in all countries. Additional insurance is generally purchased on a per-participant basis, and some countries carry a heavy insurance cost.
- **Monitoring activities should be considered and budgeted for accordingly:** Clinical trials must be adequately monitored for protocol and GCP compliance by a suitably trained/qualified monitor. Consider whether your clinical trial requires any on-site monitoring visits. If yes, this task may be delegated to an in-country vendor.
- **Essential Document Management platform – Florence eBinders™:** All MCRI-sponsored international IITs are required to use the Florence eBinders platform for the management of all trial-related essential documents. Each trial is required to cover the costs associated with its use of the Florence eBinders platform.
- **FTE Allocation for tasks associated with data cleaning and data verification:** Consider whether additional FTE support is needed to fund Clinical Data Manager/s to support the Central Trial Coordinating Team in all aspects of data management and data cleaning. Your Trial Coordinator will be dedicated to overseeing trial conduct at both a local and international level and supporting the participating sites during trial conduct. Incorporating an experienced Clinical Data Manager within your Central Trial Coordinating Team to lead all data management and data cleaning activities and support related SOP development is beneficial to a trial.

Note: Some funders will not cover all of these costs (i.e. some funders will not cover the cost of insurance or fund overseas activity such as direct funding for overseas FTE), therefore alternative arrangements may need to be made to cover these costs separately.

In addition, MCRI may take a percentage of your awarded grant to cover institutional overheads and infrastructure costs to support core institutional functions.

5.2. International Sponsorship: Assigning a Local Sponsor/Legal Representative

As per ICH-GCP E6(R2), the Sponsor of a clinical trial is defined as an individual, company, institution, or organisation who takes ultimate responsibility for the initiation, management, and financing (or arranging the financing) of a trial4.

Some international trials will require assigning a Local Sponsor / Legal Representative within the jurisdiction you plan to conduct your trial in. This is dependent on the relevant regulations within the country and whether your research is subjected to those regulations. However, not all international trials will require appointment of a Local Sponsor/Legal Representative when MCRI is the sponsor. Determining whether your clinical trial activity falls under the scope of the relevant regulations within the jurisdiction is key and will save a lot of time and money during trial development.

5.2.1. Basic Sponsorship Principals

This section outlines the principles underpinning the sponsorship of studies involving one or more institutions.

a) The Sponsor is the individual or institution that takes responsibility for the initiation, management and financing (or arranging the financing) of the study. The Sponsor must satisfy itself that the study meets the relevant standards and ensure that arrangements are put and kept in place for management, monitoring and reporting.

b) Sponsors can formally delegate one or more of the elements of sponsorship for example, to the chief investigator, clinical trial unit or another third party, but the Sponsor remains

accountable for all aspects of sponsorship whether delegated or not. The Sponsor must implement procedures to ensure appropriate oversight of all delegated functions. This can be achieved by:

i. Assessing that individuals or organisations delegated sponsor functions are appropriately qualified and competent to perform those functions.
ii. Ensuring all parties are aware of their roles and responsibilities (by clearly defining them in contracts/agreements and a division of responsibilities document).
iii. Maintaining lines of communication to ensure the obligations of all parties are being met (for example by receiving progress reports).

5.2.2. Country-Specific Examples

In the UK and the EEA, non-IMP/non-Medical Device trials generally do not fall under the scope of the EU Clinical Trial Directive1 (i.e. national regulation) and hence, do not require appointment of a Local Sponsor/Legal Representative nor applications to the respective Competent Authority.

In accordance with the EU Clinical Trial Directive (Regulation (EU) No 536/2014)1, an In-Country Local Sponsor/Legal Representative is required when the Sponsor of the trial is not based within the local area1. This applies to the UK and countries within the European Economic Area (EEA). The legal representative acts as the agent of the Sponsor in the event of any legal proceedings instituted in the UK or the EEA (for example, for service of legal documents) but does not take on the legal liabilities of the sponsor5. In summary, when MCRI is the Sponsor of a trial, an In-Country Local Sponsor/Legal Representative must be appointed for IMPs being run within the UK and the EEA.

For clinical trials run within Canada, an In-Country Local Sponsor/Legal Representative may not always be required. In accordance with the Canada Food and Drug Regulations (FDR)6 , a clinical trial Sponsor may be domestic or foreign.

In Canada, a trial with a foreign Sponsor is required to have a senior medical or scientific officer who is residing in Canada appointed who will represent the Sponsor, and sign and date the application and the clinical trial attestation form. Canada also permits a Sponsor to transfer any or all of its trial-related duties and functions to a contract research organisation (CRO) and/or institutional site(s). However, the ultimate responsibility for the trial data's quality and integrity always resides with the Sponsor. Any trial-related responsibilities transferred to a CRO or institutional site should be specified in a written agreement.

5.2.3. Regulatory Resources and Tools

To assist in determining whether a clinical trial falls under the scope of the EU Clinical Trial Directive, the UK's Regulatory Agency, the Medicines and Healthcare products Regulatory Agency (MHRA), have developed an algorithm to assist researchers in answering the question[7]:

https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/949145/Algorithm_Clean__1_.pdf

For trials where it is determined that a Local Sponsor/Legal Representative is required, appropriate contracts must be executed between MCRI and the Local Sponsor/Legal Representative. This is to ensure that delegated roles and responsibilities are explicitly stated and understood by each party. To further assist in navigating the international regulatory landscape and assist in planning and implementing international clinical research, several online research tools are available:

a) https://clinregs.niaid.nih.gov/

ClinRegs[8] is an online database of country-specific clinical research regulatory information designed to assist in planning and implementing international clinical research. Countries included are based on the National Institute of Allergy and Infectious Diseases (NIAID) international clinical research priorities, namely non-EU countries.

b) http://campus.ecrin.org/

The European Clinical Research Infrastructure Network (ECRIN)[9] is an online database of European countries clinical research regulatory information designed to assist in planning and implementing international clinical research. Countries included are EU-based comprising of all 27 EU member states.

c) https://www.hhs.gov/ohrp/regulations-and-policy/index.html

The Office of Human Research Protections (OHRP)[10] in the US has published a variety of policy and regulatory guidance materials to assist the research community in conducting ethical research that is in compliance with the US Health & Human Services regulations. These include guidance documents and frequently asked questions (FAQs) addressing various topics, findings in the form of OHRP letters addressing regulatory issues, and other media including decision tree graphics and educational videos.

5.3. Protocol Design

Trial planning begins years before the start of participant enrolment/randomisation. Participating site investigators may actively contribute to the trial and protocol design which often leads to multiple investigator meetings and frequent changes. Trial planning can be even more complex when multiple countries are involved.

When planning for an international study, one must consider potential differences in the standard of care and cultural practices that could impact implementation of the protocol. For example, in England, the use of contraception cannot be mandatory for women who choose to participate in a research protocol, nor can it be mentioned in the informed consent document[2].

Refer to the CRDO Launching Pad to access the suite of MCTC Protocol Templates available for MCRI Researchers.

5.3.1. Country-Specific Protocol Addendum

Developing a single protocol to accommodate every country involved in your clinical research may not be practical and feasible, due to significant differences in standard of care practices globally. Additionally, a single protocol may not meet the requirements of individual EC's and CA's.

One way to address the differences across various jurisdictions is to develop a core protocol for all participating sites. This would be supplemented by Country-Specific Protocol Addenda to address the components/requirements specific to each jurisdiction.

Examples when a Country-Specific Protocol Addendum should be considered:

- In response to queries received from a specific Competent Authority (CA) in one country only, however, the requested changes to the protocol do not affect the other countries/jurisdictions involved in the trial.

- In response to an EC's request to use their preferred protocol template as it contains mandatory wording required by the EC, however, the mandatory wording does not apply to the other countries/jurisdictions involved in the trial.

5.3.2. Participant Population

Additional considerations regarding participant populations are outlined below:

- The funder may set specific limits on the involvement of participating countries including the number of participants recruited internationally. This will be included in the funding agreement
- In studies that include vulnerable populations, such as children/young people and adults lacking capacity, local governing legislation must be taken into account
- Potential differences (e.g. standard of care, cultural practice, and standards of literacy) should be considered when designing the protocol and participant documents

For Paediatric Research
The legal age of children and the regulatory reporting requirements for paediatric research populations differ internationally. This must be taken into consideration when planning data cleaning and reporting activities. For example, within a clinical trial setting, Japan considers adults to be persons aged 21 or over, however in the UK, persons aged over the age of 16 are considered adults.

5.4. Personal Data (Data) and Biospecimen Collection and Transfer

5.4.1. Data Collection and Data Transfer

The difference in the definition of personal data and the requirements under applicable legislation in different countries must be considered in the protocol design and as required, within the PICF. For example, the General Data Protection Regulation (GDPR)[11] in the EEA and the UK and the General Data Protection Law (LGPD)[12] in Brazil.

a) Data Collection:
   - Country master PICFs must comply with local privacy laws and include a statement noting that data will be transferred to Australia (note there is considered to be a lower level of data protection in Australia compared to the EEA and the UK under the GDPR).
   - PICFs must also disclose any onward data-transfers and data sharing.
   - When designing data capture tools, i.e. Case Report Forms (CRF), the accessibility and language used must be considered.

b) Data Transfer:
   - The transfer of data must be set up securely.
   - An agreement (usually in the form of a Data Transfer Agreement or specific clauses in a Clinical Trial Research Agreement) must be in place to cover the transfer of the data to MCRI (such agreement to be reviewed and signed off by MCRI legal team).
   - Where data is transferred to MCRI, only members of the Central Trial Coordinating Team may access and use the data (or as otherwise agreed in the relevant agreement and always in accordance with the protocol and PICF).
   - A Data Management Plan (DMP) must be completed for all clinical trials, and in some countries a Data Protection Impact Assessment (DPIA) (refer to section 4.11 for further information) will also need to be completed.

A DMP is a written document that describes the data you expect to acquire or generate during the course of your research, how you will manage, describe, analyse, and store those data, and what mechanisms you will use at the end of your project to share and preserve your data. It is also used to identify any potential risks associated with the data. A DMP should also include what data management practices/activities will be used and who will be responsible for each of these practices/activities.

Refer to the CEBU Data Management Plan for a template DMP.

For further information regarding the General Data Protection Regulation (GDPR), the following MCTC resources are available:

- MCTC106 Guidance – Principles of the GDPR & Data Protection in a Research Context – A Guideline for Researchers
- MCTC107 Guidance – GDPR Information Sheet and Quick Facts
- MCTC108 Checklist – Data Protection Checklist

For further advice regarding global Data Protection Regulations, Privacy regulations and/or the Australian Privacy Principals (APP), Central Trial Coordinating Teams should contact:

Melbourne Children's Trial Centre:	MCTC@mcri.edu.au
MCRI Privacy Officer	legal@mcri.edu.au

5.4.2. Biospecimen Collection and Transfer

Similarly to personal data collection and transfer or disclosures, the collection, processing/analysis, and transfer of biospecimens in different countries must also be considered in the protocol design and the PICFs.

- Country master PICFs should include a statement noting that biospecimens will be transferred to Australia, and/or other location/s, as applicable to your protocol.
- All locations where samples may be transferred for testing and data analysis must be disclosed within the PICF.
- Any onward transfers and data sharing must also be disclosed.

Refer to Section 4.10 below for further information regarding Biospecimen transfer processes.

5.5. Regional Lead / In-Country Lead Site / National Coordinating Centre

Please consider if a 'Regional Lead (RL) / In-Country Lead Site / National Coordinating Centre (NCC)' (hereafter referred to as In-Country Lead Site) should be selected for each country and contracted/delegated to perform additional tasks, such as coordinate and streamline the relevant EC and CA submissions on behalf of all participating sites within that country/jurisdiction.

- An In-Country Lead Site should be selected for each country and contracted to perform additional responsibilities such as acting as the main point of contact for that country (for EC and CA's). This will usually include additional payments. If this is not an option, the MCRI Central Trial Coordinating Team can retain responsibility.

- An agreement must be put in place with any In-Country Lead Site (see section 4.7 below). The agreement will need to set out a clear division of responsibilities between the MCRI Central Trial Coordinating Team and the selected In-Country Lead Site.

5.6. Identification, Feasibility and Selection of International Sites

Identification and evaluation of potential international sites is a key part of the development phase for any international clinical trial. Initially, Central Trial Coordinating Teams should reach out to potential sites to determine their interest in the trial. Follow-up occurs by inviting interested sites to complete a Site Feasibility Questionnaire.

Careful evaluation of key site qualifications, appropriate site infrastructure, previous research experience, access to patient populations and a desire to comply with the requirements of the protocol at the outset, will guide you to select only the most suitably qualified sites for inclusion in your clinical research[3]. This reduces the chance of engaging in low performing sites and gaining a better return of investment with your allocated study funds.

- The MCRI Central Trial Coordinating Team is required to perform a feasibility assessment of each international site to assess their suitability, experience, and available resources (facility, staffing and patient population) to determine the likelihood that the site:
    - Can open within reasonable timelines
    - Will meet the recruitment targets
    - Will perform the trial in accordance with the protocol and GCP regulations
    - Has adequate site infrastructure and resourcing to conduct the trial
    - Is suitably qualified and experienced
- In certain circumstances it may be appropriate for the In-Country Lead Site (where applicable) to perform the feasibility assessment of potentials sites within their jurisdiction on behalf of (or in collaboration with) the MCRI Central Trial Coordinating Team.
- The outcome of the feasibility assessment should be used to determine the priority for opening sites, due to the additional resources required to open an international site.
- Where any confidential information of MCRI is to be shared with potential sites as part of the feasibility assessment process, a Confidential Disclosure Agreement (CDA) may be required – see section 4.7 below.

5.7. Agreements

The MCRI Legal Team will facilitate the preparation and negotiation of any required agreements for your clinical research. The MCRI Legal Team have several readily available international agreements which can be used as a starting point for any new agreement required for international participating sites.

In addition to the standard Clinical Trial Research Agreement (CTRA) between the Sponsor and the participating sites, consideration will need to be given to any of the following Agreements which may apply to the type of clinical trial you are conducting:

- Confidential Disclosure Agreement (CDA): Before sharing any confidential information (including the study protocol) with a potential international site, it may be advisable for MCRI and the potential site to enter into a CDA to ensure that the potential site will keep the information being disclosed to them confidential.

- Research Collaboration Agreement (RCA): If the clinical trial and protocol design has been developed in collaboration with researchers from another institution or entity, MCRI must enter into an RCA with such other institution(s) or entity(-ies). The RCA sets out the rights and obligations of each collaboration (including, for instance, which party will enter into CTRAs with sites, which party will analyse the data and/or samples, etc).

- In-Country Lead Site Agreements: This must clearly detail the delegation of responsibilities between the Sponsor and the selected lead site in each country. The In-Country Lead Site will normally be delegated responsibilities to:

    - Prepare country-specific master PICFs.
    - Prepare all required ethics, regulatory authority and/or data protection authority applications.
    - Obtain all country-specific approvals, including any amendments and maintenance of these approvals for the duration of the trial.
    - Maintain a country level TMF (or sub-section of the master TMF)
    - Fulfil local safety reporting requirements to relevant CA and EC.
    - Fulfil local data protection authority reporting requirements to relevant CA and EC.
    - Fulfil local serious breach and urgent safety measure (USM) reporting to the relevant CA and EC.
    - Carry out monitoring activities as directed by the trial's monitoring plan including close-out activities and preparation for archiving, if delegated this function.
    - Other delegated functions as required by your clinical research.

- A Services Agreement may be the appropriate form of agreement if the third party is only providing services, and is not collaborating on the study design, or recruiting for the trial. For example, this would be appropriate for a Contract Research Organisation (CRO) or an Academic Clinical Trials Unit (CTU) engaged to prepare and submit all ethical and regulatory applications on behalf of all participating sites within the UK, but not recruiting participants into the trial. A Services Agreement may also be required for vendors providing specific services for your clinical research, for example, courier services, central pharmacy and drug distribution services, central laboratory processing services, translation services, on-site monitoring services.

- Data Transfer Agreement (DTA): Covering the transfer of data. If applicable to your clinical research and the relevant terms regarding data sharing are not already contained within an existing Agreement.

- Material Transfer Agreement (MTA): Covering the transfer of any material/s such as bio-specimens/samples. If applicable to your clinical research and the relevant terms regarding sharing of materials not already contained within an existing Agreement.

- Depending on the design of the study, other agreements may be required; for example, A Power of Attorney form (A2 Form) may be required in the Netherlands if engaging a participating site to act as a National Coordinating Centre (NCC)/In-Country Lead Site on behalf of other Dutch sites.

For further information regarding Clinical Trial Research Agreements, Central Trial Coordinating Teams should contact the following personnel:

MCRI Head of Legal:	penny.glenn@mcri.edu.au
MCRI Legal	legal@mcri.edu.au

5.8. Insurance & Indemnity

Clinical trials come with risks for the Sponsor (e.g. – if a participant suffers personal injuries or property damage, or if the research team is held liable for an error or an omission or another breach of their professional duties). As a Sponsor, MCRI must ensure that it is sufficiently protected from the financial risks

of something going wrong in the course of the clinical trial. Similarly, the participating sites will also want to be covered in case something goes wrong at their site because of an error in the protocol for instance.

There are two traditional ways to get protected from those types of risks: taking an insurance policy with a reputable insurer and requesting an indemnity from another party.

As per the Australian Clinical Trials website, the difference between insurance and indemnity cover is defined 13:

Insurance: A policy taken out by an individual or individual organisation (the insured) to cover their own risks or liabilities. The insured pays a premium for the cover which usually depends on the risk-profile and claim history of the insured and the types of activities covered.

Indemnity: An indemnity is a contractual obligation where one party promises to another party that it will pay for a loss suffered by the other party.

5.8.1. Insurance

Procurement of liability insurance is a complex and critical aspect of clinical trial start-up that is often underestimated or overlooked by the Central Trial Coordinating Teams.

Usually the Clinical Trial Research Agreement (CTRA) for an IIT includes an insurance clause providing that the Sponsor and the site must each maintain insurances necessary to cover their conduct of the clinical trial activities or the performance of their obligations under the CTRA.

There are usually three types of insurance cover that are relevant to clinical trials:

- *Medical Indemnity insurance* which covers claims seeking compensation for personal injuries arising from patient care in the context of a clinical trial or other research activities;
- *Professional indemnity insurance* which covers claims seeking compensation for an alleged breach of professional duties arising out of the provision of advice or expertise in the context of a clinical trial or other research activities; and
- *Public and product liability insurance* which covers legal liabilities arising from clinical trial activities that result in personal injury or property damage to participants.

Proof of insurance is part of the regulatory document submission and approval in some countries. As with other aspects of international clinical trials, each country has their own set of rules governing indemnity insurance[3].

MCRI holds a global master Insurance policy (Newline Group Insurance underwritten by Lloyd's globally), renewed annually, that is sufficient to cover clinical trial activities in some countries including the United Kingdom (UK) and New Zealand (NZ), although an additional premium may be payable depending on the nature of the study. However, many MCRI-sponsored trials involving international sites will not be covered under the master policy, and a separate locally-issued insurance policy will need to be purchased for each country the trial is recruiting in.

- Insurance is arranged by the MCRI Finance Consultant and MCRI Legal Team and is country and protocol specific (countries and/or protocols considered high risk in terms of clinical trial conduct will have higher insurance premiums).
- In order to purchase the Policy, a range of documents must be provided to the Insurer. This may include the trial protocol, country-specific consent forms (back-translated into English), a copy of the Clinical Trial Research Agreement for each participating site and anticipated recruitment numbers within each country.
- Maintenance of insurance cover includes but is not limited to:

- Ensuring renewal arrangements are in place to avoid lapsed cover.
- Ensuring the insurance provider is informed of protocol amendments, where applicable, and provided with copies of any updated trial protocols.
- Ensuring the insurance provider is informed if the trial exceeds its anticipated recruitment numbers in any country, as coverage is generally purchased on a per participant basis per country.
- Note: To manage insurance costs, it is possible to purchase insurance on a minimum number of participants and then increase your insurance coverage as recruitment continues. This will require close monitoring of your recruitment numbers per jurisdiction and communication with the MCRI Finance Consultant, to ensure an adequate and constant level of insurance with no lapsed policies.

5.8.2. Indemnity

Usually CTRAs for IITs include a clause that provides that each party is liable for its acts and omissions in relation to the conduct of the clinical trial. In some instances, a site might request an indemnity from the Sponsor so that it makes it easier for them to recover their loss arising from the conduct of the IIT (if any) from the Sponsor. MCRI Legal Team will review and assess whether it is appropriate for MCRI, as a Sponsor, to provide an indemnity and, where necessary, limit the scope of such an indemnity to the minimum required.

For further information regarding Clinical Trial Insurance or indemnity, Central Trial Coordinating Teams should contact the following personnel:

MCRI Head of Legal:	penny.glenn@mcri.edu.au
MCRI Finance Consultant:	neil.harker@mcri.edu.au
Melbourne Children's Trial Centre:	MCTC@mcri.edu.au

5.9. ICH-GCP, Personnel Training & Research Education

Training is important to minimise variation in data collection so that all trial information is obtained and reported in the same way across all participating sites and countries.

5.9.1. ICH-GCP

- For trials involving an IMP, the principles of GCP must be followed in accordance with the country's legislative requirement.
- For IMP trials, it is a legal requirement to follow the International Council for Harmonisation Good Clinical Practice (ICH GCP) where study data is to be used as part of a licensing application for marketing authorisation.
- For non-IMP trials, the local requirements for GCP training should be followed.
- Some country-specific courses may include GCP training as part of a larger accredited course – this is sufficient as long as it meets the TransCelerate approved minimum requirements. For example eBrok Certification in the Netherlands. Refer to the following website to check whether country-specific courses meet the GCP mutual recognition program: https://transcelerate-gcp-mutual-recognition.com/home

5.9.2. ISO 14155

- ISO 14155 has been developed by the International Organization for Standardization. It addresses GCP for the design, conduct, recording and reporting of clinical investigations

carried out in human participants to assess the safety or performance of medical devices for regulatory purposes.

- For trials involving an IMD, the principals of ISO 14155 must be followed in accordance with the country's legislative requirement.
- The TGA recognises that ISO 14155 has substantially harmonised with the Guideline for Good Clinical Practice and therefore provides an equivalent standard. It also addresses the specific requirements of investigational medical device trials.

The TGA recognises that ISO 14155 has substantially harmonised with the Guideline for Good Clinical Practice and therefore provides an equivalent standard. It also addresses the specific requirements of investigational medical device trials.

5.9.3. Personnel Training & Research Education

Training programs should be established to ensure that site investigators are well-versed in the trial's protocol and procedures and that they understand what must be done at specific time points throughout trial conduct. Traditionally, this is accomplished by arranging central or regional investigator meetings. The timing of the investigator training(s) is very important. Training a site research team too far in advance of the beginning of recruitment could compromise your research, creating a situation whereby investigators would require retraining at the point of site activation.

Knowledge of the study procedures and rules is enhanced through group discussion and training. Logistical inconsistencies and differences in practices between participating sites and different countries can be identified and planned for when group training occurs.

Effectively implementing information technology and using online training systems/training webinars may mitigate against training complexities. In addition, using regional video conferencing and online video training sessions with post-training electronic testing and certification could save time and money, in addition to creating country-specific manuals, guidelines and SOPs (where applicable) to address any local standard of care differences between jurisdictions.

5.10. Bio-Specimens: Collection and Movement of Samples for Research Purposes

A Material Transfer Agreement (MTA) will be required for the collection and movement of all samples if it has not already been incorporated in a Participating Site Agreement.

- Where the collection of biological samples is an outcome measure, each country's regulations, and requirements regarding the import/export of biological samples will need to be considered as part of the feasibility assessment,
  Note: some countries prohibit exporting biological samples, others, such as China, require special export permits which are difficult to obtain.
- Feasibility Assessments should also include capturing details on site infrastructure and resourcing around bio-specimen collection and handling, as well as, on-site processing capabilities and long-term storage capabilities, if applicable.
- Bio-specimen collection details need to be explicitly disclosed in the PICFs, including:
  - Bio-Specimen collection type
  - Collection volume/s
  - Any Genetic testing to be undertaken (if applicable)
  - Duration of bio-specimen sample storage
  - Where the samples will be sent/shipped to for processing and/or analysis
  - Any onward transfers to third parties for required analysis post processing

- Any onward transfers of the derived data from the bio-specimen analysis to third parties

- In addition, consider:
  - Engaging a local Central Lab in each jurisdiction to process the samples according to protocol requirements and set-up of laboratory logistics, if on-site processing by participating sites is not feasible
  - Provision of laboratory kits to participating centres
  - The time and cost to transport samples, including returns if applicable
  - The transport conditions to preserve integrity
  - Temperature monitoring during transport if applicable
  - Identification of samples (site identifiers must be applied to all samples)
  - Development of a Laboratory Manual to accompany the trial protocol
  - Whether you would like the right to use remaining samples and sample derivatives (e.g., stored in a biobank) for future ethically approved research purposes. If so, this should be covered in the agreement with the site, and in line with the protocol and PICFs.

5.11. Risk Assessments

A risk assessment must be performed by the MCRI Central Trial Coordinating Team for their proposed international clinical trial with recommendations for risk management measures included. These should be incorporated into risk assessment activities below:

- For MCRI-Sponsored IITs, the Central Trial Coordinating Team will complete a Risk Assessment during the MCRI Sponsorship Application and Approval process. The purpose of the Sponsorship Committee is to review IITs in order to grant sponsorship of the trial by the MCRI. Updated Risk Assessments are required at intervals as defined by the MCRI Sponsorship Committee. Refer to the MCTC037 SOP - SOP for Institutional Sponsorship Application and Approval for Sponsor-Investigator Initiated Trials (IITs) for further information on the MCRI Sponsorship Application process.
- An additional Risk Assessment is to be completed when developing the trials Clinical Monitoring Plan (CMP). Refer to the MCTC046 SOP – Monitoring Visit Activities for further information.
- Risk mitigating actions identified must be:
  - Satisfactorily addressed by the Central Trial Coordinating Team within the specified timeline
  - Reviewed routinely to ensure timely completion (for example, at 6-monthly MCRI Sponsorship Committee review meetings)
- A Data Management Plan (DMP): Refer to section 4.4.1 for a definition of a DMP. Refer to the CEBU Data Management Plan (DMP) template for further information.
- A Data Protection Impact Assessment (DPIA): A DPIA involves an assessment of the privacy risks to individuals in the collection, use and disclosure of information and is a requirement of the GDPR Regulation. DPIAs help identify privacy risks, foresee problems, and bring forward solutions. A DPIA should cover the flow of data, what the data is used for, how it is managed, and what action is needed. Refer to the MCTC106 Guidance – Principles of the GDPR & Data Protection in a Research Context – A Guideline for Researchers, which includes further details on DPIA.

5.12. Essential Document Management

As of January 2021, all MCRI-sponsored international IITs are required to use the Florence eBinders™ platform for the management of all trial-related essential documents. This should be adequately documented in the protocol and in the PICFs.

- For MCRI-sponsored international IITs, the following essential document hierarchy should be followed unless otherwise stated in the relevant Clinical Trial Research Agreements:

	Trial Master File (TMF)	Sub-Section Only Trial Master File (TMF) - Country-Specific	Site Information File (SIF)	Investigator Site File (ISF)
MCRI Central Trial Coordinating Team	✓		✓	
Regional Lead (RL) / In-Country Lead Site / National Coordinating Centre (NCC)*		✓		
Participating Site				✓

**Only if agreed to by the Regional Lead (RL) / In-Country Lead Site / National Coordinating Centre (NCC) to maintain a sub-section of the local TMF via Florence eBinders™. Otherwise, it is the responsibility of the MCRI Trial Coordinator to obtain copies of all the relevant EC and CA applications and approval letters from In-Country Lead Sites and file them accordingly in the TMF.*

5.12.1. Local Adaptation of Documents / Version Control

Global documents generated by the MCRI Central Trial Coordinating Team will require local adaptation in order to meet local governing legislation. Furthermore you will save time by establishing generic templates for participant facing communications. Once approved by all ECs as part of the initial ethics submission/application, local site participant facing communications will not require individual ECs approval during trial conduct.

Examples of documents which may require local adaptation include, but are not limited to:

- **The Trial Protocol:** MCRI Central Trial Coordinating Teams should develop a "core protocol" for use by all participating sites in each jurisdiction, and only consider developing country-specific protocol addendums to meet any local regulatory requirements which are not addressed within the core protocol. Refer to Section 4.3.1 above for further information.
- **Participant Information Sheet & Consent Forms:** Every country has its own templates for consent forms which meet local governing legislations. MCRI Central Trial Coordinating Teams should develop master country-specific consent forms for each jurisdiction, based on a global master consent form. Your In-Country Lead Site will then be responsible for reviewing and adapting, and where required translating the country-specific master consent form to ensure all local requirements have been addressed including relevant disclosures.
- **Other Patient-Facing Material:** examples include Individual Participant Facing Communication/s, Participant ID Cards, Participant Medication Diaries, Letter to Participants etc

The document should be identified with a country code as part of version control, for example:

- *UK Master Prospective Consent Form_v1.0; dated: 11 April 2021*
- *Netherlands Region-Specific Protocol Addendum_v1.0; dated: 01 Feb 2021*

Local adaptation may include additional wording required to satisfy local requirements in relation to data controls, insurance, and regulatory/legal processes. A copy of the final country-specific version of the document must be provided to the MCRI Central Trial Coordinating Teams for review and approval prior to proceeding to Ethics Committee and/or Competent Authority submission.

5.12.2. Documents that Require Translation

MCRI Central Trial Coordinating Teams must ensure that study document translations are carried out by a translator with an appropriate understanding of clinical studies and medical terminology. You must not use Google Translate to translate your trial documents.

Most ECs globally require a copy of a translation certificate to be submitted as part of the ethical submission package, therefore, it is recommended that a certified translation service is utilised for the translation of trial documents.

Documents that require translation include:

- Participant Information Sheets, Informed consent forms, Participant ID card, advertisements, letters to participants, Investigational Medicinal Product (IMP) labels, patient facing CRFs and Quality of Life (QoL) questionnaires etc.
- The translated document must be back translated into English and checked for accuracy against the master document
- The MCRI Central Trial Coordinating Teams must review the translated documents specifically for legal terms and insurance provision, if applicable i.e. within consent forms
- Care should be taken when translating data collection documents in studies where data entry is performed centrally in another country. English prompts should remain on the document to aid data entry.

MCRI have executed a Master Services Agreement with Linguistico Translation Services for the provision of translation services to MCRI researchers. Linguistico's fees for healthcare / medical translations are based on a per source word basis and a translation certificate is provided with each service provided.

Refer to the following link on the MCRI Intranet page for further information: https://intranet.mcri.edu.au/Pages/Translation-Services.aspx

5.13. Investigational Medicinal Products (IMP)/Investigational Medical Device (IMD) Considerations

5.13.1. Investigational Medicinal Products (IMP)

If an IMP is to be used, care must be taken to ensure that it can be used in the jurisdiction of each study site. Even if a drug cannot be imported into a specific country, an equivalent substitute may be available[2].

One example relates to prednisone. Some countries, including Japan, Taiwan, and the United Kingdom do not permit importation or use of prednisone manufactured in the United States. Therefore, another form of corticosteroid (locally obtained prednisolone) must be used in trials[2].

However, in some situations, an equivalent drug may not be available and initial planning around drug supply must be factored into the development phase of any CTIMP. Ideally, questions surrounding drug supply, importation permits, and availability should be asked during the site feasibility process and equivalent questions asked in the Site Feasibility questionnaire, so that any potential IMP issue can be identified and addressed early on.

In addition, if the IMP is to be supplied from a central location, shipping regulations should be thoroughly vetted before the trial is launched. The study drug or intervention may be subject to

additional local regulatory approval and different labelling requirements in terms of language, temperature control, etc. An import license may be needed, and high custom costs may result[2].

The marketing status of an IMP differs across countries, and this will need to be taken into consideration when determining requirements for:

- Importing
- Labelling
- Shipping Requirements
- Release

Based on the above, additional agreements may be required if:

- There is a local Sponsor / legal representative
- There are separate arrangements for the provision of IMP with the manufacturer at the International sites.

5.13.2. IMP Labelling Requirements

Additionally, each country has their own combination of required data elements on the trial drug label, which must be translated into local language[3].

According to Annex 13 (Table 1) of the European Commissions "The Rules Governing Medicinal Products in the European Union", there are approximately 19 data elements (e.g., Sponsor's name, Sponsor-Investigators name, IMP name, storage conditions, for "clinical trial use" phrase) that may be required on the secondary label depending upon the country[14]. Packaging and labelling of clinical trial IMP require anywhere between 20-30 weeks from design and approval of conventional booklet labels to shipping IMP kits to sites and these timelines must be factored during your trial development phase.

5.13.3. Investigational Medical Devices (IMD)

The device used in the trial must be:

- Labelled appropriately in accordance with local regulatory requirements
- Procured, distributed, calibrated, maintained, serviced throughout the duration of the study and all records maintained.

5.14. Pharmacovigilance Reporting/Safety Reporting Requirements/Regulatory Reporting Requirement Timelines

5.14.1. IMP Safety Reporting Requirements

All Site Investigators must report Serious Adverse Events (SAEs)/Serious Adverse Reactions (SARs)/ Suspected Unexpected Serious Adverse Reactions (SUSARs) to MCRI in accordance with the protocol and the Clinical Trial Research Agreement.

The In-Country Lead Site is responsible for notifying the regulatory authority and ethics committee of reportable events in accordance with local reporting requirements.

The MCRI Central Trial Coordinating Team and In-Country Lead Site must work cooperatively to prepare and submit safety reports according to local requirements. The following should be considered:

- Reference Safety Information (RSI) / Investigator Brochure (IB) may be different as a result of IMP consideration noted in section 4.12 above, as such, this could have an impact on:
    - SUSAR Reporting
    - Provision of AE/SAE Line listings
- Safety reporting requirements differ in different countries. For example, in the UK, the Medicines and Healthcare products Regulatory Agency (MHRA) requires all "UK-relevant SUSARs" to be reported, the competent authority's definition of "UK-relevant" includes:
    - SUSARs originating in the UK
    - SUSARs originating outside the UK where the Sponsor has an ongoing study in the UK involving the same medicinal product

5.14.2. IMD Safety Reporting Requirements

Unanticipated Serious Adverse Device Effects (USADEs) and other safety events involving a medical device undergoing clinical investigation should be reported according to local regulatory requirements.

5.14.3. Urgent Safety Measures (USMs)/Other Safety Reporting Requirements

All MCRI Central Trial Coordinating Teams must identify and implement Urgent Safety Measures (USMs) (may be known differently in other countries). Once an USM has been implemented the Site Investigator must inform the Sponsor within the same working day or no later than 24 hours from its implementation.

- The In-Country Lead Site must then notify their regulatory authority and ethics committee, accordingly, including any subsequent amendment(s) identified as a result of the urgent safety measure.
- The MCRI Central Trial Coordinating Teams must notify all other participating sites accordingly, including any subsequent amendment(s) identified as a result of the urgent safety measure.

5.15. Setting Up International Sites

5.15.1. Site Initiation and Regulatory Green Light

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 documentation 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 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 site can commence. This process is referred to as the 'regulatory green light'.

Furthermore, ICH E6 (R2), Sect. 5.14.2 states that the Sponsor should not supply a participating site with IMP until all required documentation is in place including a favourable opinion from the EC and CA. For a complete this of documents required before the start of a clinical trial refer to Section 8.2 of the ICH E6 (R2) guidelines[4].

- Examples of required essential documents must be in place prior to initiating a participating site are listed as follows. Note the list is not exhaustive:
    - EC Approval
    - Competent Authority Approval, if applicable
    - A signed Clinical Trial Research Agreement
    - Site Budget

- FDA 1572 Form or equivalent Statement of Investigator form (if applicable)
- Copies of CVs and Medical Licenses
- Financial Disclosure Form

- Site initiation can only take place after the MCRI Central Trial Coordinating Team are satisfied that the site has obtained all regulatory, ethics and institutional approval and have completed set up activities.
- The Green Light Approval Form must be completed and signed-off prior to the initiation meeting, as part of regulatory green light procedure.
- Initiation meetings can be led by the MCRI Central Trial Coordinating Team but may be delegated to the In-Country Lead Site if it has been agreed in the lead site agreement. Initiation of international sites and training to study-specific activities can take place by videoconference.

Refer to the MCTC034 Template – Green Light Approval Form for a checklist of the required documents collated during site initiation and required on file prior to initiating a participating site.

5.15.2. Site Monitoring/Sponsor Oversight of International Sites

Monitoring activities of international participating sites must be included and accounted for in the Clinical Monitoring Plan (CMP) for your trial.

- The frequency and the type of monitoring activities may be agreed upon between the In-Country Lead Sites and MCRI Central Trial Coordinating Team, to ensure that all local monitoring requirements are met
- All international sites are expected to participate in remote monitoring activities as a minimum. An on-site visit whether routine or for-cause may be delegated to the In-Country Lead Site or an appropriate third-party vendor, pending execution of a Service Agreement
- Close-Out Visits (COV) can be performed remotely or on-site, if determined as necessary. Close-out activities may be delegated to the In-Country Lead Site or an appropriate third-party vendor, pending execution of a Service Agreement
- The CMP must be generated by the MCRI Central Trial Coordinating Team in accordance with the MCTC046 SOP – Monitoring Visit Activities.

5.16. MCRI Sponsored IITs with a Local Sponsor/Legal Representative

For studies where the MCRI Central Trial Coordinating Team has delegated (via an appropriate agreement) the management of the trial in a particular country to a Local Sponsor/Legal Representative the following also should also be noted:

The Local Sponsor/Legal Representative usually assumes all legal responsibilities according to local regulations in relation to:

- Obtaining CA approval before recruitment commences
- Obtaining EC approval before recruitment commences
- Obtaining and maintaining EC and local site-level approvals (if applicable) for their own site
- Reporting SUSARs, USADEs, Urgent Safety Measures (where applicable)
- Fulfilling safety and annual reporting requirements to CA and EC
- Fulfilling End of Trial reporting requirements
- Implementation of a Quality Management System (QMS), including monitoring, if delegated to do so
- Retention of a sub-set of study documents via the eTMF
- Site management responsibilities if multi-centre, including participating site agreements, EC approval, if delegated to do so

- For IMPs and IMDs, ensure investigational product provision is arranged and the IMP is labelled in the local language and in accordance with local requirements

MCRI as Sponsor must ensure:

- The communication/escalation pathway is established with the Local Sponsor/Legal Representative
- Access to data is possible for monitoring/audit purposes
- That it is permitted to audit compliance with the Clinical Trial Research Agreement.

5.17. Research Support

For further advice regarding setting up International clinical trial sites and any of the procedures outlined within this SOP, Central Trial Coordinating Teams should contact the following personnel:

SUPPORT	DEPARTMENT	CONTACT
International Trial Development Support	Melbourne Children's Trial Centre	MCTC@mcri.edu.au
Clinical Trial SOPs, Documents, Templates and Forms	Clinical Research Development Office	CRDO.info@mcri.edu.au
Legal Advice	MCRI Legal Team	Legal@mcri.edu.au
Insurance Advice	MCRI Finance Consultant – Neil Harker	Neil.Harker@mcri.edu.au
Data Protection Regulations, Privacy regulations and/or the Australian Privacy Principals (APP) Advice	Melbourne Children's Trial Centre MCRI Legal Team	MCTC@mcri.edu.au Privacy@mcri.edu.au

6. ASSOCIATED DOCUMENTS

- MCTC037 SOP - SOP for Institutional Sponsorship Application and Approval for Sponsor-Investigator Initiated Trials (IITs)
- MCTC035 Template – Sponsorship Application Form and Risk Matrix
- MCTC056 SOP – Study Start Up for Clinical Trials
- MCTC146 SOP – Regulatory Green Light Approval
- MCTC034 Template – Regulatory Green Light Approval Form
- MCTC005 SOP – Safety Monitoring and Reporting Procedure for MCRI-Sponsored Investigator Initiated Trials (IITs) of Medicines/Medical Devices
- MCTC123 SOP – Management of Non-Compliance: Protocol Deviations and Serious Breaches
- MCTC046 SOP – Monitoring Visit Activities
- MCTC047 Template – Clinical Monitoring Plan template
- CEBU Template - Data Management Plan template
- MCTC079 SOP - Data Sharing and Access Procedure for the Release of Data from MCRI Sponsored Investigator-Initiated Clinical Trials
- MCTC090 Form - Transfer of Data Form
- MCTC091 Template - Data Sharing Plan template
- MCTC012 Guidance – Trial Master File (TMF) Filing Guidance
- MCTC011 Guidance – Site Information File (SIF) Filing Guidance
- MCTC011 Guidance – Investigator Site File (ISF) Filing Guidance
- MCTC106 Guidance – Principles of the GDPR & Data Protection in a Research Context – A Guideline for Researchers
- MCTC107 Guidance – GDPR Information Sheet and Quick Facts
- MCTC108 Checklist – Data Protection Checklist

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

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.

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

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

Clinical Trial
The World Health Organisation (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 of an Investigational Medicinal Product (CTIMP)
A Clinical Trial of an Investigational Medicinal Product (CTIMP) is a study that looks at the safety or efficacy of a medicine/foodstuff/placebo in humans, as defined by the Medicines for Human Use (Clinical Trials) Regulations 2004.

Clinical Trial Research Agreement
An agreement between the Sponsor and a participating site that sets out the rights and obligation of each party in relation to the conduct of a clinical trial.

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 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 IITs, 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.

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 Site
A lead or participating site located outside of Australia.

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/Coordinating Principal Investigator.

Investigator-Initiated Trials (IITs)
Trials where the investigator initiates and organises a trial 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.

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.

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.

Local Sponsor/Legal Representative
If a Sponsor of a CTIMP is not established in the UK or the EEA/EU, it is a statutory requirement to appoint a legal representative based in the country for the purposes of the trial.

The Local Sponsor/Legal Representative:

- May be an individual person or a representative of a corporate entity
- Does not have to be a legally qualified person
- Should be willing to act as the agent of the Sponsor in the event of any legal proceedings instituted (e.g. for service of legal documents)
- Should be established and contactable at an address in the UK or EEA/EU
- Does not assume any of the legal liabilities of the Sponsor(s) for the trial by virtue of the role of legal representative and does not therefore require insurance or indemnity to meet such liabilities; but
- May in some cases enter into specific contractual arrangements to undertake some or all of the statutory duties of the Sponsor in relation to the trial, in which case the legal representative would also be regarded as a co-sponsor and would then require insurance or indemnity cover.

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.

MCRI Sponsorship Committee
The MCRI Sponsorship Committee is responsible for reviewing and determining applications for MCRI to act as Sponsor for Investigator-Initiated Trials conducted on the Melbourne Children's campus. As an additional responsibility, the MCRI Sponsorship Committee reviews requests from external (non-MCRI) researchers for access to data collected in MCRI-sponsored IITs and is authorised to make decisions regarding such requests where the study in question no longer has an active MCRI custodian. The Sponsorship Committee includes senior representatives from MCRI's MCTC, Finance, Legal and Grants Divisions. The Sponsorship Committee meets monthly.

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

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.

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 (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 GCP.

8. REFERENCES

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2. Minisman G, Bhanushali M, Conwit R, et al. Implementing clinical trials on an international platform: challenges and perspectives. *J Neurol Sci*. 2012;313(1-2):1-6. doi:10.1016/j.jns.2011.10.004 https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3254780/

3. Lai J, Forney L, Brinton DL, Simpson KN. Drivers of Start-Up Delays in Global Randomized Clinical Trials. *Ther Innov Regul Sci*. 2021;55(1):212-227. doi:10.1007/s43441-020-00207-2 https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7505220/

4. 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

5. NHS Sponsorship Principals: https://www.ct-toolkit.ac.uk/routemap/sponsorship/downloads/sponsorship_principles_V5Jun16.pdf

6. Canada Food and Drug Regulations (FDR): https://laws-lois.justice.gc.ca/PDF/C.R.C._c._870.pdf

7. Medicines and Healthcare products Regulatory Agency CTIMP Algorithm: https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/949145/Algorithm_Clean__1_.pdf

8. NIAID ClinRegs website: https://clinregs.niaid.nih.gov/

9. European Clinical Research Infrastructure Network's (ECRIN) website: http://campus.ecrin.org/

10. The Office of Human Research Protections (OHRP) website: https://www.hhs.gov/ohrp/regulations-and-policy/index.html

11. General Data Protection Regulation (GDPR): 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://eur-lex.europa.eu/legal-content/EN/TXT/HTML/?uri=CELEX:32014R0536&from=EN

12. Brazilian General Data Protection Law (LGPD): https://iapp.org/media/pdf/resource_center/Brazilian_General_Data_Protection_Law.pdf

13. Australian Clinical Trials - Frequently Asked Questions: Indemnity and insurance arrangements for clinical trials in Australia: https://www.australianclinicaltrials.gov.au/sites/default/files/files/FAQ%20insurance%20and%20indemnity%20requirements%20for%20clinical%20trials.pdf

14. European Commission EudraLex – The Rules Governing Medicinal Products in the European Union: Volume 4 – EU Guidelines to Good Manufacturing Practice, Annex 13: Investigational Medicinal Products. https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-4/2009_06_annex13.pdf

DOCUMENT END