SOP 21 Study Start Up for University of Melbourne Sponsored Clinical Trials

1.1 Purpose

The purpose of this Standard Operating Procedure (SOP) is to describe the procedures for setting up a new investigator-initiated clinical trial sponsored by the University of Melbourne, or where the University of Melbourne is a participating site involved in an externally sponsored trial where the external Sponsor has delegated certain Sponsor responsibilities to the University of Melbourne, to ensure that a consistent approach is taken from protocol development through to site initiation and activation.

This SOP identifies prerequisites for:

- Trial planning and design
- Preparing and writing your trial protocol and consent forms
- Obtaining the required approvals in order to commence the trial i.e. ethics committee and/or regulatory approvals
- Trial Registry submission
- Management of Essential Documents (ED)
- Clinical Trial Research Agreements (CTRAs) and other Agreements
- Insurance and Indemnity Requirements
- Investigational Product (IMP)/Medical Device (IMD) Planning and Preparing
- Biospecimen and Research Sub-Study Planning
- Preparing and developing your Safety Monitoring & Reporting Plan
- Preparing and developing your Clinical Monitoring Plan (CMP) and Risk Assessment
- Data and Data Collection Tools planning including the requirement for a Data Management Plan (DMP)
- Preparing, planning, and conducting your Site Training i.e. Site Initiation; and
- Site Activation and the Regulatory Green Light Process.

1.2 Scope & Responsibilities

This SOP applies to all staff involved in developing and conducting University of Melbourne sponsored investigator initiated trials (IITs) Sponsor-Investigators/Coordinating Principal Investigators (CPIs), Principal Investigators (PIs), Associate/Sub-Investigator(s), central trial coordinating teams/research coordinators and other staff involved in research duties. This SOP is applicable to all University of Melbourne sponsored IITs conducted in Australian and/or international sites.

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

As not all clinical trials are the same, it is important that consideration is given to the nature and complexity of the trial to ensure all appropriate set up activities are carried out.

Furthermore, this SOP should be reviewed early in the protocol development phase to ensure all aspects of study start-up are captured.

- Additional SOPs and guidance documents referenced within this document should be reviewed early in the start-up process to determine those which are relevant and appropriate to your trial.
- Most SOPs are accompanied by corresponding templates to assist Researchers with developing their projects.
- Clinical trials must be conducted in accordance with GCP in order to ensure human subject safety and data integrity.

1.3 Procedure

a) Protocol and Consent Form Development and Internal Team Approval Process

Protocol Development

Trial planning begins years before the start of participant enrolment/randomisation. Many key stakeholders may actively contribute to the trial and protocol design which often leads to frequent protocol changes and the need to manage many different draft versions of the protocol. Furthermore, trial planning can be even more complex when multiple countries are involved.

The Sponsor-Investigator/CPI will be responsible for inviting expressions of interest and for ultimately selecting members of the Central Trial Coordinating Team / Trial Steering Committee (TSC). The members will be involved in protocol development from conception to completion.

The protocol should be written collaboratively with the trial statistician involved in all aspects of the development of the protocol. Recommendation is to engage with MCRI's Clinical Epidemiology and Biostatistics Unit (CEBU) or the University of Melbourne's Methods and Implementation Support for Clinical and Health (MISCH) from the outset as they provide specialised biostatistics, epidemiological methods, and data management advice.

Once the draft protocol has been written, it should be distributed to for review and comment. The draft protocol review team should include one or more individuals in each of the following categories:

- Sponsor-Investigator/Coordinating Principal Investigator (CPI)
- Co-Investigators
- Trial Statistician
- Database Manager, if applicable
- Clinical Data Manager, if applicable
- A consumer representative
- Various key stakeholders from participating sites i.e. key collaborators

The process for review and update of the protocol during this development stage should be specified early on. Identify the person(s) responsible for the management of protocol drafts, for integration of comments from multiple sources into one version, and for version control:

- Identify the process for distributing documents and reviewer comments.
- Identify who and how decisions about protocol changes will be made.
- Develop a communication plan that may include convening regularly scheduled meetings (e.g., teleconferences) with protocol reviewers to discuss proposed changes prior to implementation.
- Minute discussions from such meetings to record any critical decisions or outcomes.

Please refer to the MCCT SOP-15 Document Management and Version Control for the recommended version control process. In brief, draft documents should include both a version date and a version number. Versions prior to approval will begin with 0.1 and the number will be incremented with each new draft; dates will be updated with the new issuance date. Please ensure that all document headers and footers are updated for each new draft.

A separate process for authoring, tracking, and approving protocol amendments should also be established during study start-up.

Participant Information and Consent Forms (PICFs) Development

The content of your Participant Information and Consent Forms (PICFs) are highly dependent on the content of the trial protocol, therefore, their development should begin in earnest as soon as the protocol procedures and trial-associated risks are well described.

PICF documents should be prepared using the NHMRC PICF templates suited to your type of study, as well as, in accordance with the requirements of the local HREC. For multi-site studies, consider developing an Australian master consent form using NHMRC PICF templates. In short, master copies are developed by the Sponsor-Investigator/CPI in collaboration with the Trial Coordinator. They are centrally, ethically approved and allow space for participating sites to include site-specific changes, as required by site regulatory requirements.

For multi-site, international trials, consider developing a world-wide master consent forms which can be easily tailored to suit the regulatory landscape/jurisdiction of where you intend to conduct the trial. Often individual HRECs have unique requirements for PICFs, and it is likely that significant modifications of the initial worldwide master PICF may be required.

The process for review and update of the initial master PICFs during their development stage should also be documented similarly to the development and review/approval of the protocol.

The PICF review team is likely to be a subset of the protocol review team. At a minimum, the Sponsor-Investigator/CPI, central trial coordinator, and coinvestigators should review the master PICF. Additionally, members of the University of Melbourne Legal team may also review the PICF documentation in large-scale, multi-site international trials, and will communicate any relevant comments to the Sponsor-Investigator/CPI, central trial coordinator or delegate.

b) Central/Lead-Site Approvals

It is the responsibility of the Sponsor-Investigator/CPI (or delegate) to ensure that the appropriate approvals are in place at all sites before the Site Initiation Visit (SIV) is held and before recruitment commences at any participating site.

Ethical approval and/or governance authorisation is required as well as additional approval pathways described below.

University of Melbourne Clinical Trials Review Committee Approval

- All investigator-initiated clinical trials developed and conducted by the University of Melbourne require a specifically named sponsor, in this case, the University of Melbourne.
- The Clinical Trial Review Committee reviews and grants sponsorship for IITs conducted at sites within Australia. For sponsorship of international sites additional consideration is required.
- The University of Melbourne does not support individual members of staff to personally act as the sponsor of a clinical trial.
- The Clinical Trial Review Committee requires Investigators to submit their IIT protocol and supporting documentation for review prior to commencement of the trial at any participating centres.
- The Clinical Trial Review Committee submission and review process does not duplicate the Research Ethics and Governance process; it exists in parallel.
- The Clinical Trial Review Committee does not assess scientific quality, research merit or ethical acceptability of the trial design. The review by the Clinical Trial Review Committee focuses on the business risk of the trial and, in particular, undertakes a review of the risk management mitigation strategies outlined for the trial.

Human Research Ethics Committee Review and Approvals

Follow local Human Research Ethics Committee (HREC) guidelines for creation and submission of materials and documents.

Under the National Mutual Acceptance (NMA) scheme, the scientific and ethical review by an Australian Public Health Organisation HREC that has been certified by the NHMRC will be accepted by all other Australian site HRECs. Additional sites will therefore only require Research Governance Office (RGO) approval (i.e. site-level approval), and not review by the site's HREC. Research that cannot be accepted under the NMA scheme includes, but is not limited to:

- Projects involving persons in custody or staff of the jurisdictional Justice Health departments
- Projects specifically affecting the health and wellbeing of Aboriginal and Torres Strait Islander people and communities
- Projects involving access to coronial material
- First Time in Human, Phase 0 and Phase 1 clinical trials (in NSW and SA only)

Other jurisdiction-specific exemptions may apply. Please check if any of these apply to your project. In such cases, the approval of one HREC within a jurisdiction may be accepted by the other HRECs within the same jurisdiction. For multi-site studies, it is conceivable that a participating site HREC, other than that of the lead-site, may recommend or request changes to the protocol that are not consistent with the protocol that has been accepted at other sites. In some instances, HRECs have asked that the protocol be placed into the local HREC's protocol template. It is not feasible or good practice to have different protocols operational at different sites for the same study – all sites must be operating the same version of the protocol to allow for consistent data collection.

If the HREC continues to require a particular protocol change, then it will likely be necessary to amend the protocol at the other participating sites as well. Otherwise consider developing and submitting a Region-Specific Addendum (RSA) for the centre concerned.

The protocol, PICF, and other relevant study related materials must be approved by the governing HREC and RGO (where applicable) before that site can proceed to be trained and initiated.

Scientific, Departmental or Local Research Committee Reviews and Approvals

A participating site may require that the protocol and PICF be reviewed by a scientific, departmental, or other local research committee and/or local review committee. This review is often conducted prior to or in parallel with the local HREC/RGO review.

c) Regulatory Requirements

It is the responsibility of the Sponsor-Investigator/CPI (or delegate) to ensure that the appropriate regulatory approvals are in place before the Site Initiation Visit (SIV) is held and before recruitment commences. All sites require ethical approval and/or governance authorisation but there are other regulatory processes that may also apply, and these are described below.

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

The TGA must be notified of any medicines and/or devices being used in clinical trials to allow access to these unapproved goods under the CTN scheme, in the following situations:

- If the medicine or device is not registered on the Australian Register of Therapeutic Goods (ARTG), or
- If the medicine or device is being used outside the conditions of its registration/ being used outside its approved indication (i.e. as listed in the TGA approved Product Information)

The scheme requires that the Sponsor lodges a notification and provides assurance that all the necessary parties have approved the study to start. The CTN is lodged with the Therapeutic Goods Administration (TGA) via the TGA's online portal. This includes Clinical Trial Approval (CTA).

For University of Melbourne sponsored clinical trials, the responsibility for CTN lodgement is delegated to the University of Melbourne Clinical Trial Governance team. The Clinical Trial Governance team will lodge a CTN application only after receiving evidence of ethics approval for the site(s) listed in the notification.

Trial Registration

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

The University of Melbourne has a central ClinicalTrials.gov account managed by the Clinical Trial Governance team. Registry entries are to be drafted by the research team and once sponsorship has been confirmed the draft can be reviewed and submitted by Clinical Trial Governance.

The process for registering trials can take some time. It is therefore recommended that the trial registration is submitted to the registry at least 21 days before the anticipated date of first participant enrolled.

d) Trial Plan, Start-Up Checklist & Timeline and Delegation of Responsibilities

It is critical to establish a study plan that identifies all the required activities that must be completed during the start-up process. The plan should also identify dependencies between various activities so that the central trial coordinating team understands the impact of one set of activities on another.

Identify all Parties and Clarify Responsibilities

Ensure that all study start-up activities are explicitly assigned. A Central Team Roles & Responsibilities Matrix can be used to support this goal. This matrix includes a comprehensive list of research activities and a means to identify the relevant individual responsible for each activity.

Prepare Trial Timeline and Track Start-Up Activities

Once the full set of study activities is identified and an individual owner of each activity is established, a study start-up timeline or activities tracking tool should be prepared.

There are project management software programs available that support the development of a start-up timeline and Gantt charts including Microsoft Project. Other project management applications may also be used.

Conduct Regular Team Meetings

Regular meetings with the Central Trial Coordinating Team, including the Sponsor Investigator/CPI and any key stakeholders during the study start-up phase is essential and will facilitate study organisation, communication, and tracking of progress toward site initiation and activation.

A recommendation is to establish recurring fortnightly meetings between the Central Trial Coordinating Team, the Sponsor-Investigator/CPI and any key stakeholders early on during the trial development phase.

- A running Agenda should be prepared and disseminated prior to each meeting and meeting minutes documented and any follow-up action items assigned to team members accordingly. This document acts both as minutes from previous meetings and an agenda for the upcoming meeting.
- Previous meeting minutes capture study announcements & updates, action items, and decisions. This one document retains items from all previous meetings, so that the one file is a complete archive for meeting minutes.

Regardless of the choice of study start-up tracking tool, it is strongly recommended that a tracking tool is prepared early in the start-up process, maintained vigorously during the process, and discussed regularly at team meetings, so that implications of missed target dates or activities can be illuminated.

e) Other Trial Process Documentation

The provision of supplementary trial documents to assist participating sites in conducting the trial should also be factored into the development and start-up phase of any clinical trial. These documents are developed in a collaborative approach generally within the Central Trial Coordinating Team, i.e. the Sponsor-Investigator/CPI and Trial Coordinator in collaboration with the biostatistician will develop the Statistical Analysis Plan (SAP). The following are examples of some supplementary documents that may need to be considered for your study.

Manual of Procedures (MoP)

A Manual of Procedures (MOP), sometimes also referred to as a Manual of Operations (MOO), is a handbook that guides a trial's conduct and operations and contains administrative and technical information about study conduct.

It is supplementary to the trial protocol and details a trial's organisation, operational, recruitment, screening, enrolment, randomisation, intervention procedures and follow-up procedures, data collection methods, data flow, and quality control procedures. Procedures in the MOP should be followed with the same degree of vigour as those documented in the protocol.

A MOP will facilitate consistency in protocol implementation and data collection across participants and participating sites. Use of a MOP increases the likelihood that the results of the study will be scientifically credible and provides reassurance that participant safety and scientific integrity are closely monitored.

The MOP must be reviewed carefully in conjunction with the protocol by members of the Central Trial Team in advance of study start up, and then throughout study conduct as the manual is updated.

The MOP must be modified whenever a change in the protocol is necessitated, or a study step needs to be refined or re-defined for clarity and safety.

CRF Completion Guidelines (CCGs)

CRF Completion Guidelines (CCGs) is a supplementary document to assist participating sites with completing eCRF data entry in a step-by-step manner. CCGs are drafted concurrently in line with the CRF and the trial protocol.

The purpose of well written and comprehensive CCGs is to increase data accuracy and consistency, provide traceability for decisions made during data collection, and decrease downstream work including data queries, monitoring questions, and audit findings.

The CCGs must be prepared and reviewed carefully in conjunction with protocol requirements and the CRFs, by members of the Central Trial Team and Data Management representatives, in advance of the first site initiation meeting being held, and then throughout study conduct as the CCGs are updated.

CCGs must be modified whenever a change in the CRF is necessitated, or a data entry requirement needs to be refined or re-defined for clarity.

Pharmacy Manual

A Pharmacy Manual is a supplementary document to assist Pharmacy Staff at participating sites with preparing and dispensing the trial's Investigational Product (IP). Pharmacy Manuals are drafted concurrently in line with protocol and trial randomisation requirements.

The purpose of a well written Pharmacy Manual is to ensure standardised ordering, accountability, storage, preparation, dispensing and destruction of IMP across participating sites, and decrease downstream work including monitoring questions, and audit findings.

The Pharmacy Manual must be prepared and reviewed carefully in conjunction with protocol requirements, by members of the Central Trial Team and representatives from Pharmacy Department, in advance of the first site initiation meeting being held, and then throughout study conduct as the Pharmacy Manual is updated.

Pharmacy Manuals must be modified whenever a change is necessitated.

Research Laboratory Manual

A Research Laboratory Manual is a supplementary document to assist participating sites in the collection, processing, accountability, storage and shipping of biological samples for research sub-studies which may form part of a clinical trial protocol. Lab Manuals are drafted concurrently in line with protocol and research sub-study requirements.

The purpose of a well written Research Laboratory Manual is to ensure the standardised collection, processing, accountability, storage and shipping of biological samples for research sub-studies across participating sites, to ensure viable samples are obtained for downstream research applications and research sub-studies.

The Research Laboratory Manual must be prepared and reviewed carefully in conjunction with protocol and research sub-study requirements, by members of the Central Trial Team and representatives from any Central Laboratory, in advance of the first site initiation meeting being held, and then throughout study conduct as the Laboratory Manual is updated.

Research Laboratory Manuals must be modified whenever a change is necessitated.

Other Trial Manuals

In addition to the above supplementary documentation to be generated to support the trial protocol and conduct of the study, the following are examples of some additional manuals that may need to be considered for your study:

- Randomisation Manual
- Radiation Manual
- Others identified as needed as per requirements of the study protocol.

The above supplementary manuals must be developed and finalised prior to the first site being activated to recruitment if they are deemed applicable to your trial.

f) Management of Essential Documents

In accordance with Good Clinical Practice (GCP), essential documents (ED) are those documents that "individually and collectively permit evaluation of the conduct of a study and the quality of the data produced".

- Some essential document's should be filed only at the participating site in what is referred to as the Investigator Site File (ISF)
- Whilst others only need filing within sponsor-level files in what is referred to as the Trial Master File (TMF)
- Remaining documents, i.e. the majority of essential documents, should be maintained ultimately in both locations

Trial Master File (TMF)

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

For multi-centre trials, the Sponsor-Investigator/CPI or delegate is responsible for setting up and maintaining a TMF Site Information File (SIF) for each site participating in the trial before each site commences recruitment. Please note that the SIF is a subsection of the TMF and contains essential documents relating to an individual site.

The TMF and SIF must be maintained in a ready state to allow for audit, inspection and/or monitoring on request, and to ensure that they are archived appropriately at the end of the

trial. At the trial's completion, the TMF should be archived along with any other essential documents that were stored outside the TMF.

g) Clinical Trial Research Agreements & Other Agreements

The sponsor of a trial must enter into a clinical trial research agreement (CTRA) with each participating site documenting the obligations of each party with respect to the conduct of the trial and outlining any payments that will be made to the site.

A number of template CTRA's have been developed through a collaboration between the Victorian Managed Insurance Authority (VMIA), state health departments and industry. These templates are widely used within Australia and provide a uniformly accepted set of terms so the agreements can be prepared and executed without the need for substantial review. These templates are the preferred templates for use in all VIC public hospitals and non-for-profit medical research institutes.

The Research, Innovation and Contracts team reviews, negotiates, arranges approvals for, and the signing of, the University's research-related contracts. In addition to the standard Clinical Trial Research Agreement (CTRA) between the Sponsor (the University of Melbourne) 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 the University of Melbourne and the potential site to enter into a CDA to ensure that the potential site will keep the information being disclosed to them confidential.
- 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.

Clinical Trial Research Agreement (CTRA)

The three main templates are available via the *Medicines Australia website*.

- Collaborative OR Cooperative Research Group (CRG) template:

  This template should be used when a collaborative or cooperative group (CRG) acts as the sponsor of a clinical trial. A CRG is defined as 'an academic and/or non-commercial collaborative research group'. This template should be used to contract with sites when the University of Melbourne initiates and sponsors a trial or acts as the local sponsor for a non-commercial consortium.

- Commercially Sponsored Trials template:

  This template is for use by a commercial sponsor (e.g. an Australian pharmaceutical company or Australian subsidiary of an international pharmaceutical company) only. It should not be issued by University of Melbourne for any University of Melbourne sponsored clinical trials.

- Contract Research Organisation (CRO) template:

  This template is for use by a contract research organisation (CRO) engaged to act as the local sponsor of a clinical trial by an international sponsor. The University of

Melbourne may receive this agreement from a CRO, but it would not normally be issued by the University of Melbourne to a participating site.

- Medical Device Trial CTRA template: The Medical Technology Association of Australia has developed a separate CTRA template suitable for trials of medical technologies. The above Medicines Australia Agreements should not be used for device trials.

h) Insurance and 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, the University of Melbourne 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:

- 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.

Insurance and Indemnity cover for Clinical Trials in the Public Sector

In the public sector, each State and Territory provides indemnity or insurance coverage in relation to their clinical trial activities. The arrangements are implemented and managed through a State or Territory agency and may take the form of insurance or an indemnity fund or a self-insurance scheme.

Clinical trials coverage is usually a subset of the medical indemnity or professional indemnity coverage. Details for the Victorian scheme can be found at: Victorian Managed Insurance Authority (VMIA).

Insurance for University of Melbourne Sponsored Trials

The sponsor of a trial is required to maintain an adequate level of insurance for legal liability to pay damages or compensation as a result of any claim or claims made by research participants for bodily injury caused by any act, error or omission in connection with clinical trials.

The University of Melbourne maintains insurance cover for its liabilities in relation to the conduct of clinical trials by University of Melbourne staff. Research carried out by VIC public health system personnel is generally covered by the VIC Government's self-insurance scheme, the Victorian Managed Insurance Authority (VMIA), although the extent of this cover may vary for Staff Specialists and Visiting Medical Officers and would need to be confirmed on a case-by-case basis.

Registered medical practitioners are required by law to maintain (at their own cost) membership of a Medical Defence Organisation and be fully insured for their own malpractice,

professional errors, omissions, or negligence. Some policies require the practitioner to notify their insurer of specific research involvement before the cover applies.

International Sites and Insurance

If the clinical trial is being conducted with the involvement of international participating sites, it is recommended that you provide a list of the overseas sites involved in the trial to the prior to implementing any site agreements to request confirmation that the clinical trials insurance policy will extend to cover the trial activities at sites internationally.

i) Sourcing and Supply of Investigational Medicinal Product (IMP)/ Investigational Medical Device (IMD)

Studies that include an Investigational Medicinal Product (IMP) or Investigational Medical Device (IMD) must ensure that the source and supply of products is clearly established and defined early on in the trial development phase. It may be possible to source these through standard commercial means, or via special arrangements with a pharmaceutical / medical device company. Regardless, researchers must consult with pharmacy, and document their plan for sourcing their product.

Documentation around sourcing of supply of IMP or IMDs must be included within the trial protocol, as well as detailed information included in a section within the trials corresponding Manual of Procedures (MoP) document (for Medical Devices) or as a stand-alone separate Pharmacy Manual for IMPs.

An appropriate Agreement must be in place between the IMP/IMD supplier and the University of Melbourne overall for the trial i.e. a master contract in place between the University of Melbourne and drug company if IMP or medical device is being supplied by a pharmaceutical company.

In multi-centre trials, arrangements must be in place for shipping of IMP to participating sites, if the IMP is being supplied by the pharmaceutical company; options may include:

- The pharmaceutical company shipping IMP direct to the participating sites.
- The pharmaceutical company shipping IMP direct to a central pharmacy. Then central pharmacy is then tasked with managing and shipping IMP to the participating sites.

IP Labelling Requirements have been addressed during the trial development phase. This includes generation of secondary labels in accordance with Annex 13 for use on IMP.

If Hospital stock/commercial stock is being utilised, this should be clearly stated within the trial protocol and any supporting trial documentation such as a Pharmacy Manual.

Master IMP Accountability documents should also be considered and prepared and disseminated to participating sites Pharmacy departments prior to the commencement of recruitment.

j) Biospecimen and Materials Management

Clinical trials that include biospecimen collection as part of research sub-studies must ensure that the procedures for the collection, handling, processing, storage, and tracking of samples is clearly established and well-documented. Often this documentation will be included within the trial protocol, as well as detailed information included in a section within the trials corresponding Manual of Procedures (MoP) document or as a stand-alone separate Research Laboratory Manual.

Consider whether samples require processing at a central research laboratory, rather than local on-site processing. If processing is to be completed centrally by a nominated laboratory,

then arrangements must be in place with that laboratory prior to the start of recruitment for the processing to occur:

- Clear detailed instructions must be included in a corresponding Research Laboratory Manual informing sites on how to collect and prepare the sample for shipping to the central laboratory.
- Timelines for shipping samples to the central laboratory must also be detailed.

Arrangements must be in place for shipping of laboratory kits to participating sites if kits are being supplied by the University of Melbourne Central Trial Coordinating Team.

Kits should include all the necessary consumables needed to collect and complete any necessary on-site processing of samples, i.e. blood collection tubes, specimen aliquoting tubes and labels, packing and shipping materials, and participant information or instructional material (where applicable) etc.

Detailed instructions on how to order and re-order biospecimen kits, collect and process samples and how to store and/or ship samples must all be included in a corresponding Research Laboratory Manual produced during the trial development phase.

Laboratory kits should be on-site prior to conducting the site initiation visit with each participating site.

k) Safety Monitoring and Reporting

Clinical trials must be monitored for safety and potential risk to the participant. Monitoring of participant safety must be described in the trial protocol and be in accordance with the Sponsor organisation's written procedure for safety reporting.

Every trial should consider appointing independent medical monitors to facilitate the appropriate oversight, review, and assessment of all reported safety events to ensure the safety of study participants.

It is, however, best practice to also develop a Safety Monitoring and Reporting Plan (SMP), when appropriate. This plan must be reviewed and approved by Sponsor-Investigator/CPI, and all nominated Medical Monitors assigned to review safety events.

The protocol should specify if all AEs or only a subset of AEs (i.e. protocol-defined AEs, AEs of Special Interest (AESIs), Adverse Drug Reactions (ADRs)) are to be collected for the trial. In addition to Adverse Event (AE)/Serious Adverse Event (SAE) monitoring, the protocol and SMP should detail the process for monitoring and reporting Unanticipated Problems (UPs), Significant Safety Issues (SSIs) and Urgent Safety Measures (USMs).

Central Trial teams should provide Site Investigators with a template safety reporting form to facilitate the reporting of SAEs, SUSARs/URSAEs and USMs to the Sponsor. The additional information requested on the Expedited Safety Report form will assist the Sponsor Investigator/CPI fulfil their requirements for onward reporting of safety events to the HREC, site PIs, the TGA and other regulatory bodies (if applicable).

Safety Monitoring and Reporting Plan (SMP)

Every trial must identify the most appropriate level of safety monitoring activities. The Sponsor-Investigator/CPI (or delegate) is responsible for establishing a process on how to monitor the safety of participants during the trial. These processes must be documented in the trial's Safety Monitoring and Reporting Plan (SMP).

This purpose of a SMP is to clearly delineate who is responsible for reporting and reviewing clinical trial safety data, how this process will occur, and to describes the safety reporting, safety monitoring and intervention-vigilance requirements for the clinical trial.

A safety monitoring plan (SMP) should include the role and responsibilities of the Sponsor-Investigator/CPI, site Principal Investigator (PI), the Sponsor and any independent Safety Monitors and/or safety oversight committees (i.e., Data Safety Monitoring Committee (DSMC)) and clearly describe the process of review and reconciliation of safety events.

The safety monitoring plan should be written after the Sponsor-Investigator/CPI has identified all the risks to participant safety and established how they will manage and monitor these risks. This information should also be documented in the trial specific Risk Assessment and Risk Management Plan.

The safety monitoring plan should be reviewed on an ongoing basis and may be updated throughout study conduct to reflect changes in the way safety monitoring is performed or in the event there is a change in the risks to participant safety and updated where appropriate.

Independent Safety Monitors (ISMs)/Medical Monitors (MMs)

The Sponsor requires that each clinical trial have a system implemented to facilitate the appropriate oversight, review, and assessment of all reported safety events to ensure the safety of study participants. In this case, independent medical monitors should be considered.

Independent Safety Monitors (ISMs) / Medical Monitors are an independent physician/clinician or other appropriate expert with relevant expertise in the therapeutic area in question, whose primary responsibility is to provide independent safety monitoring of clinical trials.

ISMs/MMs should have no direct involvement in the conduct of the study. Furthermore, ISMs/MMs should not have financial, proprietary, professional, or other interests that may affect impartial, independent decision-making.

The main aim of reviewing safety events is to:

- Review all reported SAEs within the required regulatory authority timelines.
- Assign relatedness and expectedness of the reported event.
- Identify any safety issues that may put participants at increased risk.
- Take the appropriate course of action for any identified risk/safety concern.
- Notify the Sponsor, HREC/IRBs, and participating sites of any safety issues identified.
- Satisfy reporting requirements to regulatory bodies i.e., the TGA and other relevant regulatory authorities.

ISMs/MMs are tasked with the following responsibilities:

- Evaluate and assess AEs and SAEs and review safety reports for relatedness and expectedness.
- Review and evaluate information relevant to product/intervention safety.
- Confer with other nominated Independent Safety Monitors (ISM) / Medical Monitors (MMs).
- Participate on safety oversight committees, where applicable

Data Safety Monitoring Board (DSMB)

A Data Safety Monitoring Board (DSMB), also known as a Data Safety Monitoring Committee (DSMC), may be used to provide additional safety oversight of a trial. DSMB's are an independent group of experts charged with reviewing study data for data quality and integrity, adherence to the protocol, participant safety, study conduct and progress, and making determinations regarding study continuations, modifications, and suspensions/terminations.

The DSMB must have at least three members including, at minimum, one content related or therapeutic area expert and a biostatistician.

DSMBs are an important component of many monitoring plans but are not required for all clinical trials. It will depend on the complexity and endpoints of the trial, the participant population and the safety profile of the intervention.

Alternative monitoring structures may be used when a DSMB is not necessary.

l) Risk Assessments and Clinical Monitoring Plan (CMP)

Risk Assessments

A risk assessment must be performed by the University of Melbourne Central Trial Coordinating Team for their proposed clinical trial with recommendations for risk management measures included.

Risk mitigating actions identified must be satisfactorily addressed by the Central Trial Coordinating Team within the specified timeline and reviewed routinely to ensure timely completion.

A data management plan 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.

Clinical Monitoring Plan (CMP)

Monitoring is defined as the act of overseeing the progress of a clinical trial, and of ensuring that it is conducted, recorded, and reported in accordance with the protocol, SOPs, the principles of GCP, and the Medicines for Human Use (Clinical Trails) Regulations - where applicable.

The purpose of monitoring is to verify that:

- The rights and well-being of the human subjects are protected
- The reported trial data are accurate, complete, and verifiable from source documents
- The conduct of the trial is in compliance with the currently approved protocol/amendment(s), GCP and the applicable regulatory requirements

Monitoring is an integral role in the quality control of a clinical trial and is designed to verify the ongoing quality of the study. Clinical Monitoring Plans (CMP) must be developed and finalised prior to the first site being activated to recruitment.

m) Data Collection and Data Management

Good data management practices are essential to the success of a clinical trial because they help to ensure that the data collected is complete, reliable, and accurate. The objectives of good clinical data management are to ensure:

- That the trial database is complete, accurate and a true representation of what took place in the trial.
- That the trial database is sufficiently clean to support the statistical analysis and its interpretation.

Below are some key points to consider when developing your data collection tools and surveillance of data to ensure a clean data set is achieved at the end of the trial.

Data Collection Tools and Designing the Data Collection Instrument

Standardisation will save time and errors in the design of forms and computer programs used in the data processing and statistical analysis.

A CRF should be used to document each participant's study data for all clinical trials. This may be a paper or an electronic document and should cover all of the data required for the study as described in the protocol.

CRF design should begin in parallel with protocol development as the CRF is essentially the data capture system for the protocol. CRFs should be developed using the principals of Good Clinical Data Management Practices (GCDMP) or using other best data management practices, including but not limited to:

- Data Minimisation: collect only necessary data that will be used for analysis and avoid collecting redundant data.
    - Avoid collecting patient identifiers, such as initials and Hospital Numbers, to reduce the risk of re-identification of trial participants.
- Clear and Concise CRFs: Keep the end-user in mind so that CRFs are quick and easy for site personnel to complete and clear in what is being asked.
- Standardised Variable Terminology: Consider naming variables using Clinical Data Interchange Standards Consortium (CDASH) terminology.
    - CDASH establishes a standardised way to collect data consistently and provides guidance to assist in developing CRFs for domains/variables that are commonly used for the majority of the clinical trials across a range of therapeutic areas.
- Avoid "Free Text" Fields: Free text fields are difficult to analyse and will require coding before being analysed and included in the final analysis.
    - Use 'yes/no' checkboxes whenever possible or provide 'drop down' lists / radio buttons of possible options.
- User Acceptance Testing (UAT): Ensure that all members of the Central Trial Coordinating Team have adequately reviewed and undertaken UAT of the CRFs before they are finalised. This includes the Trial Statistician to ensure that the data needed to analyse the trial endpoints is being adequately collected.
- CRF Completion Guidelines: Prepare CRF Completion Guidelines to assist site personnel in completing the CRFs.

Source Documents

Before designing a CRF it is important to know how each item of data will be collected and where it will be first recorded. Any place where the data item was recorded for the first time is known as the source document for that item of data. The main ways for recording collected study data are further outlined below.

- Data is entered directly into the CRF and therefore the CRF acts as the source Document:

  As the CRF is the first place that the data are recorded, the CRF is also considered source data. Note that data items collected directly for the purpose of the study (e.g. diary cards, participant-completed questionnaires) are also considered part of the

CRF. The protocol should identify the data items that are to be recorded directly into the CRF pages (i.e. where the data is not first entered to the participant's record).

- The participant's medical or other record is the source document:

  In this case, the data required for the study are recorded first in the participant's medical or other original records (e.g. hospital medical record, participant study progress notes, laboratory results, x-ray reports, ECG tracings) and then entered onto a paper or electronic CRF. The data on the CRF or in the database must be consistent with the original record. Note that medical or other records are independent of the study and may therefore lack precision, detail, documental consistency, and completeness as required by the study CRF.

  In practice, most studies use a combination of these two approaches, with some data recorded first into the participant's records and some data recorded directly into the CRF. It is important to specify any data items that will be recorded directly into the CRF and to list what the source document is for each item of data collected; this can be documented in, for example, a study manual or a document providing instructions on how to complete the CRF pages (often referred to as a 'CRF Completion Guide').

  All source documents must be retained in a durable and retrievable form and measures must be taken to prevent accidental or premature destruction of these documents.

Data Management Plan (DMP)

All clinical trials must have a Data Management Plan (DMP) in place to ensure compliance with good data management practices. A DMP is a written document that describes the plans for the collection and management of data throughout the lifecycle of a clinical trial and describes 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.

For effective data management, planning must begin at the time of trial design and is essential that the DMP is finalised prior to the commencement of any data collection.

A DMP should also include but is not limited to:

- What data management practices/activities will be used.
- Clearly identify the roles and responsibilities of the data management team.
- A description of the types of data being collected.
- A description of the system being used to collect/handle the clinical trial data.
- A description of how external data will be reviewed and integrated with the clinical database, if applicable.
- A description of the data archiving and data sharing intentions should also be documented.
- An overall diagram of the flow of data for your study.

Data Validation Plan (DVP)

Data validation is the process of testing the validity of data in accordance with the protocol specifications to ensure the accuracy and quality of the data. It is implemented by building several checks into a system, such as an Electronic Data Capture (EDC) platform or generating reports to ensure the logical consistency of input and stored data. All clinical trials should consider documenting their data validation activities within a DVP to ensure compliance with good data management practices.

DVPs should contain the description of the validation plan for the trial; i.e., methods for confirming that data are correct, such as range checks, valid value checks, and data cross-checks.

Data validation and edit check programs should be written to identify any discrepancies in the entered data, to ensure data validity. These programs are generally embedded in the trial's EDC and written according to the logic condition mentioned in the DVP.

A data discrepancy is defined as a data point that fails to pass a validation check. Discrepancy may be due to inconsistent data, missing data, range checks, and deviations from the protocol. In e-CRF based studies, data validation process will be run frequently for identifying discrepancies.

Data Validation Plans (DVP) must be developed in collaboration with the Sponsor Investigator/CPI, Trial Coordinator, Statistician and Data Manager and finalised prior to the first participant being enrolled into the trial and prior to any data being entered into the trial database.

Medical Coding

Medical coding assists in identifying and properly classifying the medical terminologies associated with the clinical trial. For classification of events, medical dictionaries available online are used. Technically, this activity needs the knowledge of medical terminology, understanding of disease entities, drugs used, and a basic knowledge of the pathological processes involved. Functionally, it also requires knowledge about the structure of electronic medical dictionaries and the hierarchy of classifications available in them.

Adverse events occurring during the study, prior to and concomitantly administered medications and pre-or co-existing illnesses are coded using the available medical dictionaries.

- Commonly, Medical Dictionary for Regulatory Activities (MedDRA) is used for the coding of adverse events as well as other illnesses.
- World Health Organization–Drug Dictionary Enhanced (WHO-DDE) is commonly used for coding of medications.

Medical coding helps in classifying reported medical terms on the CRF to standard dictionary terms in order to achieve data consistency and avoid unnecessary duplication. For example, the investigators may use different terms for the same adverse event, but it is important to code all of them to a single standard code and maintain uniformity in the process.

The right coding and classification of adverse events and medication is crucial as an incorrect coding may lead to masking of safety issues or highlight the wrong safety concerns related to the drug or intervention.

CRF Completion Guidelines

A CRF completion guideline is a document to assist the site investigator and study teams to complete the CRF in a step-by-step manner and is drafted concurrently in line with the CRF and protocol.

There is no standard template for CRF completion guidelines as it is study specific. Furthermore, it should be prepared in such a way that it enables participating site personnel to complete the CRFs with ease and legibility.

CRF completion guidelines should provide clear instructions to participating site personnel for accurate completion of CRFs along with clear expectations including proper instructions on handling unknown data. For example, if exact date is unknown, then use a preferred notation in the place of missing value (i.e., UK/UNK/2022).

The language used should be simple with clear instructions, concise, and easy to understand.

Other Data Management SOPs

Other SOPs required to manage and maintain the EDC which may be applicable to your clinical trial include:

- Project User Management SOP: A process to onboard and offboard users within your EDC platform.
- Project Modification SOP: A process to track and document any request for modifications to a live EDC and their implementation date.
- Query Resolution Workflow SOP: A process that outlines how you intend on tracking and managing Data Clarification Requests (DCRs) to and from participating sites for the trial.
- Data Deletion SOP: A process that describes the steps taken to securely delete/remove trial data from the trial database, if permitted within the requirements of the protocol.
- Database Locking SOP: A process that outlines steps taken to determine a final and clean dataset at the end of the trial and request to lock the database in order to undertake the final analysis.
- Data Anonymisation SOP: A process that describes the steps taken to anonymise and prepare trial data for sharing with other researchers.
- Data Transfer SOP: A process that describes the steps taken to securely and appropriately transfer trial data to other researchers.

Development of Standard Operating Procedures (SOPs) to Support the Conduct of a Study

An SOP is a detailed, written instruction, the purpose of which is to achieve uniformity in the way a specific task or function is performed. It is a controlled document and is created through a controlled documentation process, meaning that it cannot be modified without going through a documented process of approval.

Researchers involved in a clinical trial may identify the need for a new SOP, or a deficiency in an existing SOP. This signals the need to initiate the creation of a new SOP or revision of an existing SOP.

Sponsor-Level SOPs:

- Support a strong clinical research environment and provide the best way to help your site stay compliant
- Helps ensure compliance with the applicable regulations, policies, and GCP guidelines that are common to clinical research of all types
- Contribute to the overall success of the study
- Support consistency and uniformity across participating research teams/sites
- Enhances research quality, efficiency, data reliability and patient safety
- Ensures everyone on the clinical trial team is following the same rules

These trial-specific SOPs must be in place prior to commencing recruitment, to ensure uniformity is achieved across the trial. Examples of trial-specific SOPs include the following, noting the list is not exhaustive:

- Randomisation SOP

- Emergency Unblinding SOP
- Data Deletion SOP

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

Once the Central Trial Coordinating Team determine that a participating site is sufficiently prepared to begin participant recruitment (i.e. all essential documents have been collated, the CTRA has been signed and all required regulatory approvals have been obtained), a Site Initiation Visit (SIV) must be scheduled with the participating site to initiate the trial.

A Site Initiation Visit (SIV) or Study Start-Up meeting is an organised meeting with the participating site to discuss the new protocol before the trial is ready to commence screening and enrolling potential patients. It also serves as training for the protocol of interest.

- All members on the study (i.e. everyone listed on the Signature and Delegation Log) should attend the meeting including Pharmacy, and supporting services as appropriate, once all the agreements and approvals are in place.
- All study team members should have reviewed the protocol prior to the meeting as it lays the groundwork for the study and allows all team members to ask any questions, they may have prior to commencing the study.
- The study start up meeting should be scheduled soon before the anticipated activation date, so information discussed at the visit is retained by the site staff. If the study is not initiated at a participating site within 8 weeks of the SIV, appropriate material from the SIV will be reviewed again with the site staff.
- At the meeting, the protocol should be reviewed with procedures highlighted and attention drawn to any study specific SOPs. At the meeting, Participant Information and Consent Forms (PICFs) should also be reviewed. The clinical trial team should be reminded of the importance of research governance (if applicable) and adherence to the principles of Good Clinical Practice (GCP), relevant legislation and subsequent amendments (if applicable).
- The SIV is also a good opportunity for the study staff to complete the signature and delegation of authority log, training log, SIV attendance log and ensure their Curriculum Vitae (CV) and GCP Training Certificate is signed and on file within the sites ISF.
- Site Initiation Visits and subsequent monitoring visits should be outlined in a Clinical Monitoring Plan (CMP)

n) "Regulatory Green Light Approval" to Commence Recruitment

A participating site must only be activated to commence recruitment once it has met all the requirements for Regulatory Green Light Approval (outlined in the above steps). When all these requirements have been met, the participating site may be activated to commence screening and enrolling.

1.4 References & Useful Links

- ICH Guideline for Good Clinical Practice
  https://www.tga.gov.au/resources/publication/corporate-reports/ich-guideline-good-clinical-practice

- NHMRC: National Statement on Ethical Conduct in Human Research (2007) - Updated 2018 *https://www.nhmrc.gov.au/about-us/publications/national-statement-ethical-conduct-human-research-2007-updated-2018*
- 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%20a nd%20indemnity%20requirements%20for%20clinical%20trials.pdf
- Australian Clinical Trial Handbook – Guidance on conducting clinical trials in Australia using 'unapproved' therapeutic goods *https://www.tga.gov.au/resources/guidance/australian-clinical-trial-handbook*
- NHMRC: Safety Monitoring and Reporting in clinical trials involving Therapeutic Goods *https://www.nhmrc.gov.au/about-us/publications/safety-monitoring-and-reporting-clinical-trials-involving-therapeutic-goods*

1.5 Supporting Templates and Work Instructions

- MCCT SOP 04 - Protocol and Investigational Brochure Requirements
- MCCT SOP 05 - Communication with HREC, RGO, Sponsor and Institution's Insurer
- MCCT SOP 06 - Site Initiation
- MCCT SOP 07 - The Study Master File
- MCCT SOP 08 - Case Report Forms and Source Documents
- MCCT SOP 09 - Participant Informed Consent Process and Documentation
- MCCT SOP 10 - Handling and Shipping of Biological Substances (Cat B) and Dangerous Goods
- MCCT SOP 11 - Management of Investigational Product
- MCCT SOP 12 - Safety Data Monitoring and Reporting Requirements for Clinical Trials
- MCCT SOP 13 - Site Close-Out and Archiving
- MCCT SOP 14 - Data Sharing and Access Procedure for the Release of Data for IITs
- MCCT SOP 15 - Document Management and Version Control
- MCCT SOP 16 - Clinical Trial Registration of Investigator-Initiated Trials
- MCCT SOP 17 - Copying and Certifying Essential Documents
- MCCT SOP 18 - Establishing International Clinical Trials
- MCCT SOP 19 - Regulatory Green Light Approval for Clinical Trial Site Activation

- MCCT SOP 20 - Monitoring Visit Activities for Clinical Trials of Investigational Products

1.6 Glossary

Case Report Form (CRF)	Data collection tool used to record all the protocol required information to be reported to the sponsor on each research/trial participant. The CRF may be paper or electronic.
Clinical Monitoring Plan (CMP)	In accordance with the Integrated Addendum to ICH E6 (R1) Guideline for Good Clinical Practice E6 (R2) Section 5.18.7 (that was formerly adopted by the TGA with annotations on 8 February 2018), the Sponsor should develop a monitoring plan that is tailored to the specific human subject protection and data integrity risks of the trial. This plan must describe the monitoring strategy, the monitoring responsibilities of all the parties involved, the various monitoring methods to be used, and the rationale for their use.
Central Trial Coordinating Centre	A group of University of Melbourne researchers organised to coordinate the planning, development, operations and conduct of a University of Melbourne sponsored IIT, multi-centre, clinical trial.
Clinical Research Coordinator	A research worker who works at a clinical research site under the immediate direction of a Principal Investigator, whose research activities are conducted under Good Clinical Practice guidelines. May also be called a research coordinator, study coordinator or (for clinical trials research) a clinical trial coordinator.
Clinical Trial	Clinical trials can involve investigating new or existing medicines, medical devices and other medical or non-medical interventions. For example, a clinical trial could involve new drugs, medical devices, biologicals, vaccines, surgical and other medical treatments and procedures. Psycho-therapeutic and behavioural therapies help service changes, preventative care strategies and educational interventions are also examples of clinical trials. Researchers might also conduct clinical trials to evaluate diagnostic or screening tests and new ways to detect and treat disease.
Clinical Trial Approval (CTA)	Formally known as Clinical Trial Exemption (CTX), 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 reviewing 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 reviewing ethics committee has enough scientific and technical expertise to review the proposed use of the unapproved therapeutic good(s). Most investigator-initiated trials would be in this category.

Corrective and Preventive Action Plan	A Corrective and Preventive Action (CAPA) plan is a quality system plan and incorporates: • Identifying the issue, including scope and impact • Identifying the root cause of the issue – how/why it occurred • Identifying actions to prevent recurrence of the issue (corrective action) or, identify actions to prevent an issue from occurring (preventive action) • Documenting that the corrective actions/preventive actions were completed • Documenting that the corrective/preventive action has resolved the problem
Data Safety Monitoring Board (DSMB)	An independent and multi-disciplinary group established by the trial sponsor to review, at intervals, accumulating trial data, in order to monitor the progress of a trial and to make recommendations on whether to continue, modify or stop the trial for safety or ethical reasons.
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.
Food and Drug Administration (FDA)	A department of the United States of America's federal government responsible for the control and supervision of food safety, tobacco products, dietary supplements, medications, vaccines, biopharmaceuticals, blood transfusions, medical devices, electromagnetic radiation emitting devices (ERED), cosmetics, animal foods & feed, and veterinary products.
Good Clinical Practice (GCP)	A standard for the design, conduct, performance, monitoring, auditing, recording, analyses, and reporting of clinical trials that provides assurance that the data and reported results are credible and accurate, and that the rights, integrity, and confidentiality of trial participants are protected.
Human Research Ethics Committee (HREC)	A body which reviews research proposals involving human participants to ensure that they are ethically acceptable and in accordance with relevant standards and guidelines. The National Statement requires that all research proposals involving human participants be reviewed and approved by an HREC and sets out the requirements for the composition of an HREC.
International Conference on Harmonisation (ICH)	The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) is unique in bringing together the regulatory authorities and pharmaceutical industry to discuss scientific and technical aspects of drug registration.
Investigator	A person responsible for the conduct of the clinical trial at a trial site. There are four types of Investigator roles used to describe Investigators with different levels of responsibility for the conduct of clinical trials. These are described below. • Sub-Investigator Any individual member of the clinical trial team designated and supervised by the Principal investigator at a trial site to perform critical trial-related procedures and/or to make important trial-related decisions (e.g., associates, residents, research fellows). May also be referred to as Associate Investigator. • Coordinating Principal Investigator (CPI) If a study is conducted at more than one study site, the Principal Investigator taking the additional responsibility for coordination of the study across all sites in a region is known as the Coordinating Principal

	Investigator (CPI). This role applies to externally sponsored studies where the Sponsor may be a collaborative research group, commercial Sponsor or an institution. The Principal Investigator at each site will retain responsibility for the conduct of the study at their site. • Principal Investigator The PI is the person responsible, individually or as a leader of the clinical trial team at a site, for the conduct of a clinical trial at that site. As such, the PI supports a culture of responsible clinical trial conduct in their health service organisation in their field of practice and, is responsible for adequately supervising his or her clinical trial team. The PI must conduct the clinical trial in accordance with the approved clinical trial protocol and ensure adequate clinical cover is provided for the trial and ensure compliance with the trial protocol. • Sponsor-Investigator An individual who both initiates and conducts, alone or with others, a clinical trial, and under whose immediate direction the investigational product is administered to, dispensed to, or used by a participant. The term does not include any person other than an individual (eg, it does not include a corporation or an agency). The obligations of a sponsor investigator include both those of a sponsor and those of an investigator.
Investigator-Initiated Trials (IITs)	A clinical trial which is initiated and organised by an Investigator i.e. an individual rather than a collaborative group, company, or organisation. In these cases, the Investigator will take on the role of the trial sponsor and will then be responsible for the extensive GCP and regulatory requirements associated with both the management and conduct of the trial.
Investigational Medicinal Product (IMP)	A pharmaceutical form of an active ingredient or placebo being tested or used as a reference in a clinical trial, including a product with a marketing authorisation when used or assembled (formulated or packaged) in a way different from the approved form, or when used for an unapproved indication, or when used to gain further information about an approved use.
Investigational Medical Device (IMD)	A device that is the subject of a clinical study designed to evaluate the effectiveness and/or safety of the device.
Investigator Site File (ISF)	Filing repository controlled by the site Principal Investigator. It is held at the trial site and contains all the essential documents necessary for the site trial team to conduct the trial as well as the essential documents that individually and collectively permit evaluation of the conduct of the trial at the site and the quality of the data produced.
Manual of Procedures (MOP)	A handbook which supplements the protocol to guide a study's conduct and facilitate consistency in protocol implementation and data collection across participants and clinical sites. Also commonly known as Manual of Operations (MOO).
Monitor	A person appointed by the Sponsor to undertake the role of monitoring for the trial. Monitors should be appropriately trained and should have the scientific and/or clinical knowledge needed to monitor the trial adequately.
National Health and Medical Research Council: (NHMRC)	An independent statutory body within the portfolio of the Australian Minister for Health and Ageing responsible for allocating funding for, and directing, health and medical research, ethics and advice.
Participant	A participant is a person that is the subject of the research.

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.
Protocol	A document that describes the objective(s), design, methodology, statistical considerations, and organization of a trial.
Protocol Deviation	A protocol deviation is any breach, divergence or departure from the requirements of GCP or the clinical trial protocol.
Recruitment	Recruitment of participants for a research project (known as a study) is the process where people are identified and contacted for further discussion, provide informed consent, are screened and (where eligible) enrolled in a study.
Regulatory Green Light	Prior to authorising the start of a clinical trial and the initiation of research 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'.
Research	"Includes at least investigation undertaken to gain knowledge and understanding or to train researchers" (National Statement on Ethical Conduct in Human Research 2007 [Updated May 2015]). For the purpose of this guidance, research includes any research that requires submission to and approval from an HREC and/or research governance office. This may include (but is not limited to) observational research, clinical trials, quality assurance projects and laboratory research.
Site Activation	The point in time when all initial requirements have been satisfied and a site may begin to enrol subjects into the study.
Site Initiation Visit (SIV)	The meeting designed to prepare and train the participating site team for conducting the study. The meeting includes (at a minimum) the site Principal Investigator, other sub-investigators, site study coordinator/research nurse, other site staff assuming study responsibilities, and data management representative, if applicable. The Site Initiation Visit may also include representatives from the Central Trial Coordinating Team.
Serious Adverse Event (SAE)	An adverse event is defined as serious if it: • results in death • is life-threatening • requires hospitalisation or prolongation of existing hospitalisation • results in persistent or significant disability or incapacity • is a congenital anomaly or birth defect Other important medical events will be considered an SAE when, based upon appropriate medical judgment, they may jeopardise the research participant safety and may require medical or surgical intervention to prevent one of the outcomes listed in the above definition. This can include diagnosis of cancer.
Source Data	Source data is the original recording of an item of data. "All information in original records and certified copies of original records or clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial." (Section 1.51, Notes for Guidance on Good Clinical Practice (CPMP/ICH/135/95) Annotated with TGA Comments).
Source Document	Source documents are documents which contain source data. When data is entered directly into your electronic Case Report Forms (data collection forms) or

	database, the Case Report Form/database becomes your source document for that information.
Sponsor	An individual, organisation or group taking on responsibility for securing the arrangements to initiate, manage and finance a study. For investigator-initiated trials, the University of Melbourne 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 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.
Therapeutic Good	In relation to the evaluation, assessment and monitoring done by the TGA, therapeutic goods are broadly defined as products for use in humans in connection with: • preventing, diagnosing, curing, or alleviating a disease, ailment, defect, or injury • influencing inhibiting or modifying a physiological process • testing the susceptibility of persons to a disease or ailment • influencing, controlling, or preventing conception • testing for pregnancy This includes things that are: • used as an ingredient or component in the manufacture of therapeutic goods • used to replace or modify of parts of the anatomy
Therapeutic Goods Administration (TGA)	The Therapeutic Goods Administration (TGA) is Australia's regulatory authority for therapeutic goods.
Trial Coordinator	A Trial Coordinator has a significant role in the management of the clinical trial at the Sponsor level and provides leadership in clinical trial activities to ensure that the trial is completed within budget, on time and of the highest quality. A Trial Coordinator is responsible for managing the planning, implementation, and tracking of the clinical monitoring process, administration, and start-up of the clinical trial at the participating site and maintaining an overview of the conduct of the trial at sites. Some common roles and responsibilities performed by the Trial Coordinator include: • Participate in protocol development, CRF design and clinical study report writing • Guide in the creation and development of important study documents and manuals • Conduct feasibility assessments • Develop study budgets • Oversee participant recruitment • Oversee overall trial conduct • Ensure compliance of site-staff with the trials Standard Operating Procedures • Ensures compliance to all regulatory requirements both at a local and international level • Ensures compliance to all data protection requirements both at a local and international level

	• Ensures compliance to all safety reporting requirements both at a local and international level • Conduct team meetings and site-staff training programs • Overall responsibility of the trial • Supervise in-house clinical trial staff
Trial Master File (TMF)	Filing repository controlled by the Sponsor/Sponsor-Investigator. It is the collection of essential documents that allows the Sponsor responsibilities for the conduct of the clinical trial, the integrity of the trial data and the compliance of the trial with Good Clinical Practice (GCP) to be evaluated.
Trial Management Group (TMG)	The TMG is a group of key people at the coordinating or principal site who oversee the day-today conduct and progress of a clinical trial, including safety oversight activities and/or acting on advice from other individual(s) or group(s) providing safety oversight. For many investigatorinitiated trials, the TMG performs the role of a TSC (see below) and/or the DSMB.

1.7 Revision Chronology

Document History			
Version	**Effective Date**	**Summary of Changes**	**Author**
1.0	07 January 2026	Initial Version	Renata Phyland