

MELBOURNE HEALTH	OFFICE FOR RESEARCH		
	STANDARD OPERATING PROCEDURE: SOP004		
	Protocol and Investigational Brochure: Content, Design, Amendments & Compliance		
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1. AIM

To describe the procedures related to the development protocol content, design, amendments & compliance.

To describe the procedures related to the development investigational brochure, content, design, amendments & compliance.

2. SCOPE

Applicable to all clinical research projects undertaken at Melbourne Health, including investigator initiated research, collaborative research and all phases of clinical investigation of medicinal products, devices and diagnostics.

3. APPLICABILITY

Principal Investigator/Investigator, Sub-Investigator(s) research coordinators and other staff delegated trial-related activities by the Principal investigator.

4. Background

High-quality protocols can promote proper trial implementation, reduce avoidable protocol amendments, and facilitate full appraisal of the study's scientific and ethical considerations.

Specific content of a protocol will vary depending on whether the type of research to be undertaken and if the project is an investigation is a medicinal product, device, therapeutic intervention or other research project.

Clinical trial protocols should be compliant with ICH GCP guidelines. For completeness researchers should also consider the elements of the SPIRT and The CONSORT statements when preparing clinical trial protocols.

- The [SPIRIT 2013 Statement](#) provides recommendations for a minimum set of scientific, ethical, and administrative elements that should be addressed in a clinical trial protocol. The Statement also details the scope and systematic development methods of the SPIRIT guidance. By providing evidence-based guidance on key issues to address in a protocol, SPIRIT is intended to facilitate the drafting of protocols and improve their completeness.

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- The [CONSORT](#) (CONsolidated Standards of Reporting Trials) 2010 guideline is intended to improve the reporting of parallel-group randomized controlled trial (RCT), enabling readers to understand a trial's design, conduct, analysis and interpretation, and to assess the validity of its results. This can only be achieved through complete adherence and transparency by authors.

5. PROCEDURE

4.1 Protocol content and design

Specific content of a protocol will vary depending on whether the type of research to be undertaken and if the project is an investigation is a medicinal product, device, therapeutic intervention or other research project. The description below uses the case of a medicinal product, in the case of a device therapeutic intervention or other research project the terms should be adapted appropriately and followed where applicable.

For non-interventional clinical research projects researchers should use the protocol available through the MH website (<https://www.thermh.org.au/research/researchers/ethics/submit-ethics-application>)

For Interventional trials where the investigator is responsible for the protocol design or Melbourne Health is the sponsor use the TransCelerate Biopharma Inc. common protocol template (down load from <http://www.transceleratebiopharmainc.com/assets/common-protocol-template/>) **which MUST also provide the information in this document (where applicable).**

Note: do not delete sections of the protocol template that do not apply to your project, insert the text “Not Applicable” into these sections.

****IMPORTANT: For projects where MH is the sponsor of the CTN (orCTX), the CPI/PI must book a meeting with the Office for Research prior to submission of the project for HREC or research governance review to discuss the project/requirements.**

General Information

- Protocol title, protocol identifying number, and date. Any amendment(s) should also bear the amendment number(s) and date(s).
- Name and address of the sponsor and monitor (if other than the sponsor).
- Name and title of the person(s) authorized to sign the protocol and the protocol amendment(s) for the sponsor (if applicable).

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- Name and title of the investigator(s) who is (are) responsible for conducting the trial, and the address and telephone number(s) of the trial site(s).
- A Confidentiality statement – This document is confidential and the property of Melbourne Health. No part of it may be transmitted, reproduced, published, or used without prior written authorization from the organisation.
- A Statement of Compliance – This study will be conducted in compliance with all stipulation of this protocol, the conditions of the ethics committee approval, the NHMRC National Statement on ethical Conduct in Human Research (2007) and the Note for Guidance on Good Clinical Practice (CPMP/ICH-135/95).
- Name, title, address, and telephone number(s) of the qualified physician (or dentist, if applicable), who is responsible for all trial-site related medical (or dental) decisions (if other than investigator).
- Name(s) and address(es) of the clinical laboratory(ies) and other medical and/or technical department(s) and/or institutions involved in the trial.

Background Information (as applicable)

- Name and description of the investigational product(s).
- A summary of research/findings from non-clinical studies that potentially have clinical significance and from research/clinical trials that are relevant to the research/trial.
- Summary of the known and potential risks and benefits, if any, to human participants.
- Description of and justification for the route of administration, dosage, dosage regimen, and treatment period(s).
- A statement that the research/trial will be conducted in compliance with the protocol, GCP and the applicable regulatory requirement(s).
- Description of the population to be studied.
- References to literature and data that are relevant to the research/trial, and that provide background for the trial.

Research/Trial Objectives and Purpose

- A detailed description of the objectives and the purpose of the trial.

Research/Trial Design

- The scientific integrity of the research/trial and the credibility of the data from the research/trial depend substantially on the trial design. A description of the research/trial design should include:

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- a. A specific statement of the primary endpoints and the secondary endpoints, if any, to be measured during the research/trial.
 - b. A description of the type/design of research/trial to be conducted (e.g. double-blind, placebo controlled, parallel design) and a schematic diagram of research/trial design, procedures and stages.
- A description of the measures taken to minimize/avoid bias, including:
 - a. Randomization.
 - b. Blinding.
 - A description of the trial treatment(s) and the dosage and dosage regimen of the investigational product(s). Also include a description of the dosage form, packaging, and labelling of the investigational product(s).
 - The expected duration of participant participation, and a description of the sequence and duration of all research/trial periods, including follow-up, if any.
 - A description of the "stopping rules" or "discontinuation criteria" for individual participants, parts of research/trial and entire research/trial.
 - Accountability procedures for the investigational product(s), including the placebo(s) and comparator(s), if any.
 - Maintenance of research/trial treatment randomization codes and procedures for breaking codes.
 - The identification of any data to be recorded directly on the CRFs (i.e. no prior written or electronic record of data), and to be considered to be source data.

Risk Assessment

- Complete the current Risk Assessment Guidance form located on the Office for Research website.
- The risk assessment must address all risks of the protocol and the nominated mitigation strategies.
- The risk assessment must be submitted with the HREC application (if assessed by MH HREC) and MH governance application.

Monitoring Plan

- Prepare a monitoring plan based on the risk assessment and protocol.

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- Must be submitted with the HREC application (if assessed by MH HREC) and MH governance application.

Selection and Withdrawal of Participants

- Participant inclusion criteria.
- Participant exclusion criteria.
- Participant withdrawal criteria (i.e. terminating investigational product treatment/trial treatment) and procedures specifying:
 - a. When and how to withdraw Participant from the project/trial/ investigational product treatment.
 - b. The type and timing of the data to be collected for withdrawn Participant.
 - c. Whether and how Participant are to be replaced.
 - d. The follow-up for Participant withdrawn from investigational product treatment/trial treatment.

Treatment of Participants

- The treatment(s) to be administered, including the name(s) of all the product(s), the dose(s), the dosing schedule(s), the route/mode(s) of administration, and the treatment period(s), including the follow-up period(s) for participants for each investigational product treatment/trial treatment group/arm of the research/trial.
- Medication(s)/treatment(s) permitted (including rescue medication) and not permitted before and/or during the research/trial.
- Procedures for monitoring participant compliance.

Assessment of Efficacy

- Specification of the efficacy parameters.
- Methods and timing for assessing, recording, and analysing of efficacy parameters.

Assessment of Safety

- Specification of safety parameters.
- The methods and timing for assessing, recording, and analysing safety parameters.

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- Procedures for eliciting reports of and for recording and reporting adverse event and inter-current illnesses.
- The type and duration of the follow-up of participants after adverse events.

Statistics

- A description of the statistical methods to be employed, including timing of any planned interim analysis(es).
- The number of participants planned to be enrolled. In multicentre research/trials, the numbers of enrolled participants projected for each trial site should be specified.
- Reason for choice of sample size, including reflections on (or calculations of) the power of the research/trial and clinical justification.
- The level of significance to be used.
- Criteria for the termination of the research/trial.
- Procedure for accounting for missing, unused, and spurious data.
- Procedures for reporting any deviation(s) from the original statistical plan (any deviation(s) from the original statistical plan should be described and justified in protocol and/or in the final report, as appropriate).
- The selection of participants to be included in the analyses (e.g. all randomized participants, all dosed participants, all eligible participants, evaluable participants).

Direct Access to Source Data/Documents

- The sponsor should ensure that it is specified in the protocol or other written agreement that the investigator(s)/institution(s) will permit research/trial-related monitoring, audits, HREC review, and regulatory inspection(s), providing direct access to source data/documents.

Quality Control and Quality Assurance

Ethics

- Description of ethical considerations relating to the research/trial.

Data Handling and Record Keeping

Financing and Insurance

- Financing and insurance if not addressed in a separate agreement.

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Publication Policy

- Publication policy, if not addressed in a separate agreement. Refer to Melbourne Health requirements if no external Sponsor.

Supplements

4.2 Amendments to the protocol

The investigator(s) should:

- Inform the HREC, and seek its approval, of amendments to the protocol including amendments that:
 - a. Are proposed or undertaken without prior HREC approval in order to eliminate immediate risks to participants;
 - b. May increase the risks to participants; or
 - c. Significantly affect the conduct of the research/trial.
- Inform the HREC as soon as possible of any new safety information from other published or unpublished studies that may have an impact on the continued ethical acceptability of the trial or may indicate the need for amendments to the trial protocol. Notification of the HREC is site specific and the investigator should be familiar with the processes of their ethics committee.

4.3 Protocol compliance

The investigator(s) should:

- Conduct the research/trial in compliance with the protocol agreed to by the sponsor and, if required, by the regulatory authority(ies) and which was given approval/ favourable opinion by the HREC.
- Along with the sponsor, sign the protocol, or an alternative contract, to confirm agreement.
- Not implement any deviation from, or changes to the protocol without agreement by the sponsor and prior review and documented approval/favourable opinion from the HREC of an amendment, except where necessary to eliminate an immediate hazard(s) to trial participants, or when the change(s) involves only logistical or administrative aspects of the trial (e.g., change in monitor(s), change of telephone number(s)).
- Document and explain any deviation from the approved protocol.

The investigator(s) may:

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- Implement a deviation from, or a change to the protocol to eliminate an immediate hazard(s) to trial participants without prior HREC approval/favourable opinion.

As soon as possible, the implemented deviation or change, the reasons for it, and, if appropriate, the proposed protocol amendment(s) should be submitted:

- a. To the HREC for review and approval/favourable opinion;
- b. To the sponsor for agreement and, if required; and
- c. To the regulatory authority(ies).

4.4 Investigational brochure content and design

Specific content of an Investigational Brochure will vary depending on whether the participant of investigation is a medicinal product, device or therapeutic intervention. The description below uses the case of a medicinal product, in the case of a device or therapeutic intervention the terms should be adapted appropriately and followed where applicable.

The Investigator's Brochure (IB) is a compilation of the clinical and non-clinical data on the investigational product(s) that are relevant to the study of the product(s) in human participants.

Its purpose is to provide the investigators and others involved in the trial with the information to facilitate their understanding of the rationale for, and their compliance with, many key features of the protocol, such as the dose, dose frequency/interval, methods of administration and safety monitoring procedures.

The IB also provides insight to support the clinical management of the study participants during the course of the clinical trial.

The information should be presented in a concise, simple, objective, balanced, and non-promotional form that enables a clinician, or potential investigator, to understand it and make his/her own unbiased risk-benefit assessment of the appropriateness of the proposed trial.

As part of their written application to the HREC, provide the HREC with a current copy of the Investigator's Brochure and if updated during the trial, the Investigator/institution should supply a copy to the HREC in accordance with that HRECs procedures.

In the case of a marketed product being studied, it may be acceptable to use the Product Information as a substitute for the Investigational Brochure. The ICH guidelines state:

“If the investigational product is marketed and its pharmacology is widely understood by medical practitioners, an extensive IB may not

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be necessary. Where permitted by regulatory authorities, a basic product information brochure, package leaflet, or labelling may be an appropriate alternative, provided that it includes current, comprehensive, and detailed information on all aspects of the investigational product that might be of importance to the investigator. If a marketed product is being studied for a new use (i.e, a new indication), an IB specific to that new use should be prepared.”

4.5 The Investigator Brochure should provide the following information:

Title Page

- This should provide the sponsor's name, the identity of each investigational product (i.e., research number, chemical or approved generic name, and trade name(s) where legally permissible and desired by the sponsor), and the release date. It is also suggested that an edition number, and a reference to the number and date of the edition it supersedes, be provided.

Confidentiality Statement

- The sponsor may wish to include a statement instructing the investigator/ recipients to treat the IB as a confidential document for the sole information and use of the investigator's team and the HREC.

Contents of the Investigator’s Brochure

- The IB should contain the following sections, each with literature references where appropriate:

Table of Contents

Summary

- A brief summary (preferably not exceeding two pages) should be given, highlighting the significant physical, chemical, pharmaceutical, pharmacological, toxicological, pharmacokinetic, metabolic, and clinical information available that is relevant to the stage of clinical development of the investigational product or device.

Introduction

- A brief introductory statement should be provided that contains:
- The chemical name (and generic and trade name(s) when approved) of the investigational product(s).
- All active ingredients, the investigational product (s) pharmacological class and its expected position within this class (e.g. advantages).

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- The rationale for performing research with the investigational product(s), and the anticipated prophylactic, therapeutic, or diagnostic indication(s).
- The introductory statement should provide the general approach to be followed in evaluating the investigational product or device.

Physical, Chemical, and Pharmaceutical Properties and Formulation

- A description should be provided of the investigational product substance(s) (including the chemical and/or structural formula(e)), and a brief summary should be given of the relevant physical, chemical, and pharmaceutical properties.
- To permit appropriate safety measures to be taken in the course of the trial, a description of the formulation(s) to be used, including excipients, should be provided and justified if clinically relevant. Instructions for the storage and handling of the dosage form(s) should also be given.
- Any structural similarities to other known compounds should be mentioned.

Non-Clinical Studies

Introduction

The results of all relevant non-clinical pharmacology, toxicology, pharmacokinetic, and investigational product metabolism studies should be provided in summary form.

- This summary should address:
 - a. The methodology used;
 - b. The results, and a discussion of the relevance of the findings to the investigated therapeutic; and
 - c. The possible unfavourable and unintended effects in humans.
- The information provided may include the following, as appropriate, if known/available:
 - a. species tested
 - b. number and sex of animals in each group
 - c. unit dose (e.g., milligram/kilogram (mg/kg))
 - d. dose interval

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- e. route of administration
- f. duration of dosing
- g. information on systemic distribution
- h. duration of post-exposure follow-up
- i. results, including the following aspects:
- j. nature and frequency of pharmacological or toxic effects
- k. severity or intensity of pharmacological or toxic effects
- l. time to onset of effects
- m. reversibility of effects
- n. duration of effects
- o. dose response

Tabular format/listings should be used whenever possible to enhance the clarity of the presentation.

The following sections should discuss the most important findings from the studies, including the dose response of observed effects, the relevance to humans, and any aspects to be studied in humans.

If applicable, the effective and non-toxic dose findings in the same animal species should be compared (i.e., the therapeutic index should be discussed).

The relevance of this information to the proposed human dosing should be addressed. Whenever possible, comparisons should be made in terms of blood/tissue levels rather than on a mg/kg basis.

Non-clinical Pharmacology

- A summary of the pharmacological aspects of the investigational product and, where appropriate, its significant metabolites studied in animals, should be included.
- Such a summary should incorporate studies that assess potential therapeutic activity (e.g. efficacy models, receptor binding, and specificity) as well as those that assess safety (e.g., special studies to assess pharmacological actions other than the intended therapeutic effect(s)).

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Pharmacokinetics and Product Metabolism in Animals

- A summary of the pharmacokinetics and biological transformation and disposition of the investigational product in all species studied should be given.
- The discussion of the findings should address the absorption and the local and systemic bioavailability of the investigational product and its metabolites, and their relationship to the pharmacological and toxicological findings in animal species.

Toxicology

- A summary of the toxicological effects found in relevant studies conducted in different animal species should be described under the following headings where appropriate:
 - a. Single dose
 - b. Repeated dose
 - c. Carcinogenicity
 - d. special studies (e.g. irritancy and sensitisation)
 - e. Reproductive toxicity
 - f. Genotoxicity (mutagenicity)

Effects in Humans

Introduction

A thorough discussion of the known effects of the investigational product(s) in humans should be provided, including information on pharmacokinetics, metabolism, pharmacodynamics, dose response, safety, efficacy, and other pharmacological activities:

- Where possible, a summary of each completed clinical trial should be provided.
- Information should also be provided regarding results of any use of the investigational product(s) other than from in clinical trials, such as from experience during marketing.

Pharmacokinetics and Product Metabolism in Humans

- A summary of information on the pharmacokinetics of the investigational product(s) should be presented, including the following, if available:

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- a. Pharmacokinetics (including metabolism, as appropriate, and absorption;
- b. Plasma protein binding, distribution, and elimination);
- c. Bioavailability of the investigational product (absolute, where possible, and/or relative) using a reference dosage form;
- d. Population subgroups (e.g., gender, age, and impaired organ function);
- e. Interactions (e.g., product-product interactions and effects of food); and
- f. Other pharmacokinetic data (e.g., results of population studies performed within clinical trial(s)).

Safety and Efficacy

- A summary of information should be provided about the investigational product's/products' (including metabolites, where appropriate) safety, pharmacodynamics, efficacy, and dose response that were obtained from preceding trials in humans (healthy volunteers and/or patients).
- The implications of this information should be discussed.
- In cases where a number of clinical trials have been completed, the use of summaries of safety and efficacy across multiple trials by indications in subgroups may provide a clear presentation of the data.
- Tabular summaries of adverse drug reactions for all the clinical trials (including those for all the studied indications) would be useful.
- Important differences in adverse drug reaction patterns/incidences across indications or subgroups should be discussed.
- The IB should provide a description of the possible risks and adverse drug reactions to be anticipated on the basis of prior experiences with the product under investigation and with related products. A description should also be provided of the precautions or special monitoring to be done as part of the investigational use of the product(s).

Marketing Experience

- The IB should identify countries where the investigational product has been marketed or approved.
- Any significant information arising from the marketed use should be summarised (e.g., formulations, dosages, routes of administration, and adverse product reactions).

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- The IB should also identify all the countries where the investigational product did not receive approval/registration for marketing or was withdrawn from marketing/registration.

Summary of Data and Guidance for the Investigator

This section should provide a brief summary of the fundamental requirements or information available for a particular investigational product in order to allow a quick reference for the investigator. Summaries included in this section should not replace the information to be contained in the main body of the document.

Special emphasis should be placed on provision of quick reference safety aspects in order to find information as efficiently as possible.

6. GLOSSARY

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)

International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use is a joint initiative involving both regulators and research-based industry focusing on the technical requirements for medicinal products containing new drugs.

Investigator

An individual responsible for the conduct of a research projects including clinical trials at a research/trial site and ensures that it complies with GCP guidelines. If a research/trial is conducted by a team of individuals at a research/trial site, the investigator is the responsible leader of the team and may be called the Principal Investigator. In this instance they may delegate tasks to other team members.

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Investigator's Brochure (IB)

A compilation of the clinical and non-clinical data on the investigational product(s) that are relevant to the study of the product(s) in human participants. For marketed products it may be acceptable to use the Product Information. (see 4.4 above).

Protocol

A document that describes the objective(s), design, methodology, statistical considerations, and organization of a trial.

Sub Investigator

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).

7. REFERENCES

1. [TGA Note for guidance on Good Clinical Practice \(CPMP/ICH/135/96\) annotated with TGA comments DSEB, July 2000.](#)
2. [NHMRC National Statement on Ethical Conduct in Human Research, 2007.](#)
3. [The SPIRIT Statement](#)
4. [The CONSORT Statement](#)
5. [TransCelerate BioPharma INC. Common Protocol Template](#)
6. [ICH standard investigational brochure template](#)

7. APPENDICES

Appendix 1: SOP Change Log.

Appendix 2: ICH standard investigational brochure template (separate document).

DOCUMENT END

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PPENDIX 1: SOP CHANGE LOG

<i>Version No.</i>	<i>Reason for Issue</i>
1	First issue
2	2/10/2013 Inserted Appendices 2 and 3 into SOP document
3	<p>5/9/2017: Updates include the following:</p> <ul style="list-style-type: none"> • Add background section including refereces to SPIRIT statement and CONSORT guideline. • Include link for non-interventional clinical research protocol. • Update interventional clinical trial protocol template to be the Transcelerate Biopharma Inc. protocol. • Add risk review information. • Add monitoring plan information. • Add requirement for the CPI/PI to book a meeting with the Office for Research prior to submission ethics or governance application for projects where MH is the sponsor of the CTN (or CTX) to discuss the project/requirements.

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