Western Health

STANDARD OPERATING PROCEDURE

Protocol and Investigational Brochure Content, Design, Amendments and Compliance

Standard Operating Procedure

Western Health

SOP reference	004
Version:	3.0 Dated June 2019
Effective Date	June 2019
Review Date	June 2021
Approved by	Mr Bill Karanatsios, Research Program Director
Signature and date	

Amendment History

VERSION	DATE	AMENDMENT DETAILS
2.0	04 Dec 2015	
3.0	June 2019	Updated to align with MACH SOPs

1. AIM

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

2. SCOPE

Applicable to all clinical research projects undertaken at Western Health (WH), including Investigator initiated research, collaborative research and all phases of clinical investigation for medicinal products, medical devices and diagnostics for which WH is responsible for the conduct of the trials as a site study

3. APPLICABILITY

Principal Investigator (PI), Associate Investigator(s), research coordinators and other staff delegated research/trial-related activities by the PI at WH.

4. PROCEDURE

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 SPIRIT statement 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.

4.1. Protocol content and design

Note: For project where WH is the sponsor of the Clinical Trial Notification (CTN) / Clinical Trial Exemption (CTX), the Coordinating Principal Investigator (CPI)/PI must book a meeting with the Office for Research prior to submission of the project for Human Research Ethics Committee (HREC) or Research Governance review to discuss the project/requirements.

For non-interventional clinical research projects researchers should use the protocol available on the WH website.

For Interventional trials where the investigator is responsible for the protocol design and /or WH is the sponsor they must (where applicable) provide the following information in the protocol:

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) authorised to sign the protocol and the protocol amendment(s) for the sponsor.
- Name and title of the investigator(s) who is (are) responsible for conducting the research/trial, and the address and telephone number(s) of the research/trial site(s).
- Name, title, address, and telephone number(s) of the qualified physician, who is responsible for all trial-site related medical 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 research/trial.
- **A Confidentiality statement –** This document is confidential and the property of *[Insert Name of Institution].* No part of it may be transmitted, reproduced, published, or used without prior written authorisation 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 updates) and the Integrated Addendum to ICH E6(R1): Guideline for Good Clinical Practice ICH E6(R2) Nov 2016

Background Information

- Name and description of the investigational product(s).
- A summary of findings from non-clinical studies that potentially have clinical significance and from 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, Good Clinical Practice (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 research/trial.

Research/Trial Objectives and Purpose

- A detailed description of the objectives and the purpose of the research/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:
    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 where applicable a schematic diagram of research/trial design, procedures and stages.
- A description of the measures taken to minimise/avoid bias, including:
    a) Randomisation.
    b) Blinding

- A description of the research/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 randomisation codes and procedures for breaking codes.
- The identification of any data to be recorded directly on the Case Report Forms (CRFs) (i.e. no prior written or electronic record of data), and to be considered to be source data.

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 participants from the project/trial/investigational product treatment.
    b) The type and timing of the data to be collected for withdrawn participants.
    c) Whether and how participants are to be replaced.
    d) The follow-up for participants 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.
- 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(ses).
- The number of participants planned to be enrolled. In multicentre 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 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.

Publication Policy

- Publication policy, if not addressed in a separate agreement.

4.2. Amendments to the protocol

The investigator(s) should:

- Inform the HREC and Research Governance Office (RGO), and seek its approval/authorisation, of amendments to the protocol including amendments that:
    a) Are proposed or undertaken without prior HREC approval/Governance authorisation 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 research/trial or may indicate the need for amendments to the research/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 research/trial participants, or when the change(s) involves only logistical or administrative aspects of the research/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:

- Implement a deviation from, or a change to the protocol to eliminate an immediate hazard(s) to research/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 as appropriate:
    a) To the HREC for review and approval/favourable opinion;
    b) To the sponsor for agreement if required;
    c) To the regulatory authority(ies); and
    d) To the Research Governance Office

4.4. Investigational brochure (IB) content and design

- Specific content of an IB will vary depending on whether the subject 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 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 research/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 research/trial.
- As part of their written application to the HREC, provide the HREC with a current copy of the IB and if updated during the research/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 IB. The International Conference on Harmonisation (ICH) guidelines state:

"If the investigational product is marketed and its pharmacology is widely understood by medical practitioners, an extensive IB may not 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 (IB) 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).
- 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 research/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
  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)).

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:
    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 (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).
- 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.

5. GLOSSARY

Associate Investigator

Any individual member of the clinical trial team designated and supervised by the investigator at a study site to perform critical study-related procedures and/or to make important study-related decisions (e.g., associates, residents, research fellows). Also referred to as “Sub-Investigator”.

Case Report Form (CRF)

A printed, optical, or electronic document designed to record all of the protocol required information to be reported to the sponsor on each research/trial participant.

Clinical Research Coordinators

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 “Clinical Trial Coordinator”, “Research Coordinator” or “Study Coordinator”.

Clinical Trials Notification (CTN)

A notification scheme whereby all material relating to the proposed trial, including the trial protocol is submitted directly to the HREC by the researcher at the request of the sponsor. The TGA does not review any data relating to the clinical trial.

The HREC is responsible for assessing the scientific validity of the trial design, the safety and efficacy of the medicine or device and the ethical acceptability of the trial process, and for approval of the trial protocol.

The institution or organisation at which the trial will be conducted, referred to as the 'Approving Authority', gives the final approval for the conduct of the trial at the site, having due regard to advice from the HREC.

CTN trials cannot commence until the trial has been notified to the TGA and the appropriate notification fee paid.

Clinical Trials Exemption (CTX)

An approval process whereby a sponsor submits an application to conduct clinical trials to the TGA for evaluation and comment.

A TGA Delegate decides whether or not to object to the proposed Usage Guidelines for the product. If an objection is raised, trials may not proceed until the objection has been addressed to the Delegate's satisfaction.

If no objection is raised, the sponsor may conduct any number of clinical trials under the CTX application without further assessment by the TGA, provided use of the product in the trials falls within the original approved Usage Guidelines. Each trial conducted must be notified to the TGA.

A sponsor cannot commence a CTX trial until written advice has been received from the TGA regarding the application and approval for the conduct of the trial has been obtained from an ethics committee and the institution at which the trial will be conducted. There are two forms, each reflecting these separate processes (Parts),that must be submitted to TGA by the sponsor.

Part 1 constitutes the formal CTX application. It must be completed by the sponsor of the trial and submitted to TGA with data for evaluation.

Part 2 is used to notify the commencement of each new trial conducted under the CTX as well as new sites in ongoing CTX trials. The Part 2 form must be submitted within 28 days of the commencement of supply of goods under the CTX. There is no fee for notification of trials under the CTX scheme.

Delegate

A person delegated specific but appropriate tasks in relation to the conduct of a clinical trial. Delegation must be evidenced in writing.

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.

Principal Investigator (PI)

An individual responsible for the conduct of a clinical trial at a trial site and ensures that it complies with GCP guidelines. If a trial is conducted by a team of individuals at a 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.

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 organisation of a trial.

Research Governance Office (RGO)

Site/institutional office that are accountable for the research activities conducted at their site to ensure that research is conducted according to established ethical principles, guidelines for responsible research conduct, relevant legislation and regulations and institutional policy.

Sponsor

An individual, company, institution or organisation which takes responsibility for the initiation, management, and/or financing of a clinical trial.

6. REFERENCES

1. Based on VMIA GCP SOP No.004 Version:1.0 Dated 17 September 2007
2. Based on MACH GCP SOP No.004 Version 1.0
3. Integrated Addendum to ICH E6(R1): Guideline for Good Clinical Practice ICH E6(R2) Nov 2016

4. NHMRC National Statement on Ethical Conduct in Human Research 2007.

7. APPENDICES

Appendix 1: Standard Protocol Template

Appendix 2: WH Quality Assurance Protocol Template

Appendix 3: WH Low & Negligible Risk Protocol Template

Appendix 4: Standard Investigational Brochure (Headings only)

8. AUTHORS/CONTRIBUTORS

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9. PRIMARY PERSON/DEPARTMENT RESPONSBLE FOR DOCUMENT

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