Protocol and Investigational Brochure Content, Design, Amendments & Compliance

Standard Operating Procedure

Office of Health and Medical Research
Queensland Health

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<th>SOP reference:</th>
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<td>Version number:</td>
<td>1</td>
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<tr>
<td>Effective date:</td>
<td>01 June 2010</td>
</tr>
<tr>
<td>Review due:</td>
<td>May 2011</td>
</tr>
<tr>
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<td>Approved by:</td>
<td>Dr Jane Jacobs, Director, Research Ethics and Governance Unit</td>
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Amendment History

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Based on, and with permission of the Victorian Managed Insurance Authority – VMIA GCP SOPS
Reviewed by the QH Clinical Research Coordinators Network May 2010
1 Purpose

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

2 Responsibility / Scope

This standard applies to all Queensland Health employees (including visiting medical officers, visiting health professionals, contractors, consultants and volunteers) who propose to undertake, administrate, review and/or govern human research involving Queensland Health patients and staff.

3 Applicability

Coordinating Principal Investigator / Investigator, Associate (Sub) Investigator(s) Research Coordinators and other staff delegated trial-related activities by the Principal Investigator.

4 Procedure

4.1 Protocol content and design

This section based on ICH GCP Section 6.

Specific content of a protocol will vary depending on the subject of the research. 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.

Where the investigator is responsible for the protocol design and/or is the sponsor they should (where applicable) provide the following information in the protocol:

General Information ICH GCP 6.1

- 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.
- 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).
- Name, title, address, and telephone number(s) of the qualified physician (or dentist, if applicable), who is responsible for all site research 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 ICH GCP 6.2

- Name and description of the investigational product(s). (Clinical drug / device trial only)
- A summary of findings from non-clinical studies that potentially have clinical significance and from clinical trials that are relevant to the project.
- 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). (Clinical drug / device trial only)
- A statement that the 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 project and that provide background for the study.

Project Objectives and Purpose ICH GCP 6.3

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

Project Design ICH GCP 6.4

- The scientific integrity of the study and the credibility of the data from the project depend substantially on the project design. A description of the research design should include:
  a. A specific statement of the primary endpoints and the secondary endpoints, if any, to be measured during the study.
  b. A description of the type/design of project to be conducted (e.g. double-blind, placebo controlled, parallel design) and a schematic diagram of study design, procedures and stages.
- A description of the measures taken to minimize/avoid bias, including:
  a. Randomization.
  b. Blinding.
  c. A description of the investigational interventions, including 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). (Clinical drug / device trial only)
- The expected duration of participation, and a description of the sequence and duration of all study periods, including follow-up, if any.
- A description of the "stopping rules" or "discontinuation criteria" for individual participants, parts of the project and entire project.
- Accountability procedures for the investigational product(s), including the placebo(s) and comparator(s), if any. (Clinical drug / device trial only)
- Maintenance of trial treatment randomization codes and procedures for breaking codes. (Clinical drug / device trial only)
- 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.

**Selection and Withdrawal of Participants ICH GCP 6.5**
- Participant inclusion criteria.
- Participant exclusion criteria.
- Participant withdrawal criteria (e.g., terminating investigational product treatment / trial treatment) and procedures specifying:
  - When and how to withdraw participants from the project.
  - The type and timing of the data to be collected for withdrawn participants.
  - Whether and how participants are to be replaced.
  - The follow-up for study participants withdrawn from the project.

**Treatment of Participants ICH GCP 6.6 (For clinical drug / device trials):**
- 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 trial.
- Medication(s)/treatment(s) permitted (including rescue medication) and not permitted before and/or during the trial.
- Procedures for monitoring participant compliance.

**Assessment of Efficacy ICH GCP 6.7**
- Specification of the efficacy parameters.
- Methods and timing for assessing, recording, and analysing of efficacy parameters.

**Assessment of Safety ICH GCP 6.8**
- 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 intercurrent illnesses and serious adverse events and reactions.
- The type and duration of the follow-up of participants after adverse events.

**Statistics ICH GCP 6.9**
- 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 studies, the numbers of enrolled participants projected for each research site should be specified.
• Reason for choice of sample size, including reflections on (or calculations of) the power of the trial and clinical justification.
• The level of significance to be used.
• Criteria for the termination of the 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 ICH GCP 6.10
• The sponsor should ensure that it is specified in the protocol or other written agreement that the investigator(s)/institution(s) will permit project-related monitoring, audits, HREC review, and regulatory inspection(s), providing direct access to source data/documents.

Quality Control and Quality Assurance ICH GCP 6.11

Ethics ICH GCP 6.12
• Description of ethical considerations relating to the project.

Data Handling and Record Keeping ICH GCP 6.13
• Describe how data will collected
• Method of storing data and maintenance of confidentiality
• Description of length of time data will be retained, and method of data destruction.

Financing and Insurance ICH GCP 6.14
• Financing and insurance if not addressed in a separate agreement.

Publication Policy ICH GCP 6.15
• Publication policy, if not addressed in a separate agreement.

Supplements ICH GCP 6.16
4.2 Amendments to the protocol

The investigator(s) should:

- Inform the HREC / Governance Office, ICH GCP 8.3.2 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 trial (including changes to the Inclusion / exclusion criteria).
- Inform the HREC / Governance Office 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 project or may indicate the need for amendments to the research protocol ICH GCP 5.16. Notification of the HREC is site specific and the investigator should be familiar with the processes of their ethics committee. QH HREC SOPS

4.3 Protocol to compliance ICH GCP 4.5

The investigator(s) should:

- Conduct the project 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 reviewing HREC.
- Along with the sponsor, sign the protocol, or an alternative contract, to confirm agreement (see Medicines Australia Clinical Trial Research Agreements – go to: http://www.medicinesaustralia.com.au/pages/page39.asp)
- 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 project 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:

- 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, provided that:
  a. To the HREC for review and approval/favourable opinion;
  b. To the sponsor for agreement and, if required;


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c. To the regulatory authority(ies).

4.4 Investigational brochure content and design ICH GCP 7

Specific content of an Investigational Brochure 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 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 research project 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 research project 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, the investigator must 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 HREC's 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 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 ICH GCP 7.2.1

- 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 (of the I.B.). 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 ICH GCP 7.2.2

- The sponsor may 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 ICH GCP 7.3

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

Table of Contents ICH GCP 7.3.1

Summary ICH GCP 7.3.2

- 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 ICH GCP 7.3.3

- 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 ICH GCP 7.3.4

- 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 ICH GCP 7.3.5

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 ICH GCP 7.3.6

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:

- Pharmacokinetics (including metabolism, as appropriate, and absorption);
- Plasma protein binding, distribution, and elimination);
- Bioavailability of the investigational product (absolute, where possible, and/or relative) using a reference dosage form;
- Population subgroups (e.g., gender, age, and impaired organ function);
- Interactions (e.g., product-product interactions and effects of food); and
- 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).
- 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 ICH GCP 7.3.7

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.

It should be noted that Safety Updates, when published by Study Sponsors, are deemed to form part of the IB and should be stored in proximity with the IB.

5 Glossary

**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” or “Research Coordinator”. (ARCP Definition.)

**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.

**Governance Office(r) / Function**
The Office or coordinated function within a Public Health Organisation which is responsible for assessing the site-specific aspects of research applications, make a recommendation to the District CEO / delegate as to whether a research project should be granted authorisation at that site, and overseeing that authorised research at the site meets appropriate standards (research governance).

**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 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,
one investigator should be designated as the responsible leader of the team and should be called the site 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 organization of a trial.

**Sub / Associate Investigator**

Any individual member of the clinical trial team designated and supervised by the investigator at a trial site to perform trial-related procedures and/or to make important trial-related decisions (e.g., associates, residents, research fellows, clinical research coordinators. The P.I. will designate who will be nominated as Associate Investigators for that site.

6 **References**

1. Note for guidance on Good Clinical Practice (CPMP/ICH/135/96) annotated with TGA comments DSEB, July 2000.

7 **Appendices**

Appendix 1: [ICH standard protocol template (word doc)]

Appendix 2: [ICH standard investigational brochure template (word doc)]
CONFIDENTIAL

PROTOCOL TITLE

Protocol No: XXXX
Version: XXXX
Date: XXXXX

SPONSOR

Company Name
ADDRESS
XXXXXXX
XXXXXXX
Phone: XXXXXXX

PRINCIPAL CLINICAL INVESTIGATOR

PRINCIPAL INVESTIGATOR NAME
AMENDMENTS:

1.  
2.  
3.  
4.  

ADDRESS

XXXXXXXX

XXXXXXXX

Phone: XXXXXXX
STUDY ACKNOWLEDGMENT/CONFIDENTIALITY

By signing this Protocol, the Investigator(s) acknowledges and agrees:

The Protocol contains all necessary details for conducting the study. The Investigator will conduct this study as detailed herein, in compliance with Good Clinical Practice (GCP) and the applicable regulatory requirements, and will make every reasonable effort to complete the study within the time designated.

The Protocol and all relevant information on the drug relating to pre-clinical and prior clinical experience, which was furnished by the Sponsor, Company Name, will be made available to all physicians, nurses and other personnel who participate in the conducting of this study. The Investigator will discuss this material with them to assure that they are fully informed regarding the drug(s) and the conduct of the study.

This document contains information that is privileged or confidential. As such, it may not be disclosed unless specific prior permission is granted in writing by Company Name or such disclosure is required by federal or other laws or regulations. Persons to whom any of this information is to be disclosed must first be informed that the information is confidential. These restrictions on disclosure will apply equally to all future information supplied, which is indicated as privileged or confidential.

Company Name will have access to any source documents from which Case Report Form information may have been generated. The Case Report Forms and other data pertinent to this study are the sole property of, Company Name, which may utilise the data in various ways, such as for submission to government regulatory authorities, or in publication of the results of the study.

The conduct and results of this study will be kept confidential. The results of this study may be published. Upon completion of the Study it is the intention of the parties to prepare a joint publication regarding or describing the Study and all the results therefrom and both parties shall co-operate in this regard. Where it is the intention of Company Name to file for a patent or other intellectual property right protection, publication may be deferred at the option of Company Name for up to twelve months from the date of completion of the proposed joint publication to allow Company Name to make all filings it deems appropriate.

Investigator Signatory:
PRINCIPAL INVESTIGATOR – NAME AND TITLE

Signature:

Date:

Sponsor Signatory:

COMPANY NAME SIGNATORY – NAME AND TITLE

Signature:

Date:
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ABBREVIATIONS AND DEFINITIONS OF TERMS (examples only – modify as appropriate)

AE  Adverse Event
ALT (SGPT)  Alanine Transaminase
AST (SGOT)  Aspartate Transaminase
AUC_{0-24}  Area under the concentration-time curve from time zero to 24 hours
BMI  Body Mass Index (weight in kg divided by height in m²)
C_{max}  Maximum plasma drug concentration
CIB  Clinical Investigators’ Brochure
CRF  Case Report Form
CTN  Clinical Trial Notification
ECG  Electrocardiogram
GCP  Good Clinical Practice
GGT  Gamma Glutamyl Transpeptidase
ICH  International Conference on Harmonisation
Hb  Haemoglobin
HCT  Haematocrit
IEC  Independent Ethics Committee
Hr  Hour
LFT  Liver Function Test
LLOQ  Lower Limit of Quantification
MDTS  Metered-Dose Transdermal Spray
NHMRC  National Health and Medical Research Council
® Registered Product
PK  Pharmacokinetic
SAE  Serious Adverse Event
SD  Standard Deviation
t_{1/2}  Terminal half-life = \ln 2/\lambda_z
TGA  Therapeutic Goods Administration
t_{max}  Time of occurrence of C_{max}
ULN  Upper Limit of Normal
US  United States
WBC  White Blood Cells
1 Synopsis

Study Title:

Protocol Number:

Development Phase:

Indication:

Study Drugs:

(Including test, comparator, dosage form, dosing regimen and route)

No. Participants:

No. Centres:
Study Duration:

Objectives of the Study:

Study Endpoints:
(Primary and Secondary)

Study Design:

Eligibility Criteria (Inclusion and Exclusion)

Study Procedures:
(Including pharmacokinetic (PK) sampling times)
Safety Parameters/analysis:

Laboratory Parameters/Analysis:

Total Blood Volume:

Sample Size Determination:

(If applicable)

Statistical Analyses:

(Brief Description)

Others:

(As required by the specific study)
2 Introduction

The introduction should outline all the background information and provide a justification for conducting the study in a logical, well ordered fashion. This should include: An overview of the target indication and population for the product; A summary of pre-clinical and clinical data that is relevant to the trial, including data that justifies the use of the study medication in the target indication, with literature references; A summary of the known and potential risks and benefits, if any, to human participants; And a description of, and justification for, the route of administration, dosage, dosage regimen and treatment period(s).

3 Objectives

A detailed description of the objects of the study should be provided, split in to primary and secondary objectives as appropriate.

4 Study Design

An overview of the study design should be provided. A description of the type/design of the study should be given (i.e. double-blind, placebo-controlled, parallel design e.t.c.), with a description of the population to be studied, trial treatments, periods and expected duration of each period. A specific statement of the primary and secondary endpoints should be given, and a description of measures taken to avoid bias (i.e. randomisation, blinding etc).

5 Study Population

A full description of the study population should be given, including age, sex, condition and any additional Participant descriptor as appropriate.

5.1 Number of participants

The total number of participants should be provided, along with the number of participants per specific study cohort if appropriate.

5.2 Inclusion Criteria

All Participant inclusion criteria should be listed. Criteria should be specific and unambiguous and outline a population suitable for the phase of the study.

5.3 Exclusion Criteria

All Participant exclusion criteria should be listed. Criteria should be specific and unambiguous and should take in to account any cautions and contraindications for the investigational compound(s) and study procedures.
5.4 Other Eligibility Criteria Considerations

To assess any potential impact on Participant eligibility with regard to safety, the investigator must refer to the Clinical Investigators’ Brochure (CIB) for detailed information regarding warnings, precautions, contraindications, adverse events, and other significant data pertaining to the investigational product(s) being used in this study.

6 Study Assessments and Procedures

All study assessments and procedures should be outlined in a clear, logical and unambiguous fashion. The scientific integrity of the trial and the credibility of the data from the trial depend substantially on the trial design, and interpretation of the design within the protocol. It is therefore extremely important that the protocol specifically outlines each study procedure in sufficient detail for all procedures to be performed in an identical fashion from site to site.

Procedures should be described for each phase of the study

6.1 Screening Evaluation

6.2 Study Procedures

6.2.1 Baseline (Day 0)

6.2.2 Day 1

6.2.3 Follow-Up Visit

HEADINGS TO BE TAILORED TO STUDY VISITS

6.3 Efficacy Assessments

All efficacy assessments and procedures should be outlined in detail, or referenced to a separate document or the appendices. Copies of assessment questionnaires should be appended to the protocol.

6.4 Study Restrictions

All study restrictions should be outlined in the section below, together with the duration and period of the study to which the restrictions apply.

6.4.1 Dietary

6.4.2 Smoking

6.4.3 Confinement
6.4.4 Position / Ambulation
6.4.5 Concomitant Medication
6.4.6 Other Restrictions

6.5 Safety Assessments

Procedures for all safety assessments should be detailed, or a reference provided for the procedure (e.g. a laboratory handbook etc).

6.5.1 Physical Examination
6.5.2 Vital Signs
6.5.3 12-Lead ECG
6.5.4 Laboratory Safety Testing
   6.5.4.1 Biochemistry
   6.5.4.2 Haematology
   6.5.4.3 Serology
   6.5.4.4 Drugs of Abuse
   6.5.4.5 Urinalysis
   6.5.4.6 Faecal Analysis

6.5.5 Adverse Events

The Investigator and designated study personnel will monitor each Participant for adverse events during the study. All adverse events reported between consent and final follow-up will be recorded in the case report form (CRF). The investigator or designee will ask the Participant non-leading questions in an effort to detect adverse events. Examples of this are:

“How are you feeling?”

Or

“Since you were last asked, have you felt unwell or different from usual?”

In addition, participants should be encouraged to spontaneously report any unusual feelings or sensations. See Section 8 for full details on adverse experience reporting.

6.5.6 Other Safety Assessments

Details of any other safety assessments should be provided, if applicable.
6.6 Pharmacokinetic Sampling

Schedule and procedures for pharmacokinetic sampling should be detailed, or a reference provided for the procedures (e.g. a laboratory handbook etc).

6.7 Pharmacodynamic Sampling

Schedule and procedures for pharmacodynamic sampling should be detailed, or a reference provided for the procedures (e.g. a laboratory handbook etc).

7 Investigational product(s)

7.1 Description of Investigational Product(s)

A description of all investigational products should given (including rescue medication), including dose(s), dosage regimen(s), dosage form(s), excipients and origin.

7.2 Dose Justification

A justification for the dose of investigational product(s) should be provided, with associated literature references as appropriate.

7.3 Comparator Justification

A justification for the comparator used in the study should be provided if appropriate, with associated literature references.

7.4 Administration

Specific details on the administration of each investigational product should be provided, with any precautions if appropriate.

7.5 Randomisation Procedure

7.6 Unblinding Procedure

7.7 Product Labelling

Labelling should comply with XXXX

7.8 Handling and Storage of Study Drugs

All accountability procedures for the investigational drug, including placebo and comparators should be provided, with specific storage instructions.
8  Adverse Events (AE) and Serious Adverse Events (SAE)

The investigator is responsible for the detection and documentation of events meeting the criteria and definition of an adverse event (AE) or a serious adverse event (SAE) as provided in this protocol. During the study, when there is a safety evaluation, the investigator or site staff will be responsible for detecting AEs and SAEs, as detailed in this section of the protocol.

8.1 Definition of an Adverse Event (AE)

Any untoward medical occurrence in a participant or clinical investigation Participant, temporarily associated with the use of a medicinal product, whether or not considered related to the medicinal product.

An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. For marketed medicinal products, this also includes failure to produce benefits (i.e. lack of efficacy), abuse or misuse.

Examples of an AE include:

- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.
- New conditions detected or diagnosed after investigational product administration even though it may have been present prior to the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either investigational product or a concurrent medication (overdose per se should not be reported as an AE/SAE).

Examples of an AE do not include a/an:

- Medical or surgical procedure (e.g. endoscopy, appendectomy); the condition that leads to the procedure is an AE.
- Situations where an untoward medical occurrence did not occur (social and/or convenience admission to hospital).

In this study, AEs may include pre- or post-treatment events that occur as a result of protocol-mandated procedures (i.e. invasive procedures, modification of participants' previous therapeutic regimen).

8.2 Definition of a Serious Adverse Event (SAE)

A serious adverse event is any untoward medical occurrence that, at any dose:
a) results in death

b) is life threatening

Note: The term ‘life-threatening’ in the definition of ‘serious’ refers to an event in which the Participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death if it were more severe.

c) requires hospitalisation or prolongation of an existing hospitalisation.

Note: In general, hospitalisation signifies that the Participant has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician’s office or outpatient setting. Complications that occur during hospitalisation are AEs. If a complication prolongs hospitalisation or fulfils any other serious criteria, the event is serious. When in doubt as to whether ‘hospitalisation’ occurred or was necessary, the AE should be considered serious.

Hospitalisation for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.

d) results in disability/incapacity, or

Note: The term disability means a substantial disruption of a person’s ability to conduct normal life functions. This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhoea, influenza, and accidental trauma (e.g. sprained ankle) which may interfere or prevent everyday life functions, but do not constitute a substantial disruption.

e) is a congenital abnormality / birth defect.

Medical and scientific judgement should be exercised in deciding whether reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalisation, but may jeopardise the Participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These should also be considered serious. Examples of such events are invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalisation, or development of drug dependency or abuse.

f) Any event deemed by the investigator as being a significant medical event.

8.3 Clinical Laboratory Abnormalities and Other Abnormal Assessments as AEs and SAEs

Abnormal laboratory findings (e.g. clinical chemistry, haematology, urinalysis) or other abnormal assessments (e.g. ECG, vital signs) that are judged by the investigator as clinically significant will be recorded as AEs or SAEs if they meet the definition of an AE,
as defined in Section 8.1 or SAE as defined in Section 8.2. Clinically significant abnormal laboratory findings or other abnormal assessments that are detected during the study or are present at baseline and significantly worsen following the start of the study will be reported as AEs or SAEs. However, clinically significant abnormal laboratory findings or other abnormal assessments that are associated with a disease reported in the medical history, unless judged by the investigator as more severe than expected for the Participant’s condition, or that are present or detected at the start of the study and do not worsen, will not be reported as AEs or SAEs.

The investigator will exercise his or her medical and scientific judgement in deciding whether an abnormal laboratory finding or other abnormal assessment is clinically significant.

### 8.4 Time Period, Frequency, and Method of Detecting AEs and SAEs

All adverse events will be recorded between the time of consent and the follow-up visit. Each Participant will be monitored regularly by the investigator and study personnel for adverse events occurring throughout the study. Daily during the in-clinic treatment period, the investigator or designee will enquire about AEs by asking the following non-leading questions:

At the first scheduled AE enquiry on each Day 1 (pre-dose) participants will be asked:

“How are you feeling?”

At subsequent scheduled intervals participants will be asked:

“Since you were last asked, have you felt unwell or different from usual?”

### 8.5 Recording of AEs and SAEs

When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (e.g. hospital progress notes, laboratory, and diagnostic reports) relative to the event. The investigator will then record all relevant information regarding an AE/SAE in to the CRF. It is not acceptable for the investigator to send photocopies of the Participant’s medical records to the sponsor company (Company Name Ltd) in lieu of completion of the appropriate AE/SAE CRF pages. However, there may be instances when copies of medical records for certain cases are requested by (Company Name Ltd). In this instance, all Participant identifiers will be blinded on the copies of the medical records prior to submission to (Company Name).

For each adverse event, start and stop dates, action taken, outcome, intensity (see Section 8.8.1) and relationship to study product (causality) (see Section 8.8.2) must be documented. If an AE changes in frequency or intensity during a study, a new entry of the event must be made in the CRF.
The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. In the absence of a diagnosis, the individual signs/symptoms should be documented.

All details of any treatments initiated due to the adverse event should be recorded in the Participant’s notes and the CRF.

8.6 Prompt Reporting of SAEs to Company Name

Once an investigator becomes aware that an SAE has occurred in a study Participant, he/she will immediately notify the sponsor by contacting the study monitor via telephone to notify him/her of the event. The SAE form must be completed as thoroughly as possible with all available details of the event, signed by the investigator (or appropriately qualified designee), and faxed to the study monitor within 24 hours of first becoming aware of the event.

If the investigator does not have all information regarding an SAE, he/she will not wait to receive additional information before notifying the study monitor of the event and completing the form. The form will be updated when additional information is received.

The investigator will always provide an assessment of causality at the time of the initial report as described in Section 8.8.2, “Assessment of Causality”. If data obtained after reporting indicates that the assessment of causality is incorrect, then the SAE form may be appropriately amended, signed and dated, and resubmitted to the Sponsor.

In accordance with current QH guidelines, the investigator must also notify the Reviewing Ethics Committee or site governance Office of any SAEs according the guidelines of the Ethics Committee.

The investigator, and others responsible for Participant care, should institute any supplementary investigations of serious adverse events based on their clinical judgement of the likely causative factors. This may include seeking further opinion from a specialist in the field of the adverse event. Company Name may also request extra tests. If a Participant dies, any post-mortem findings, including histopathology will be provided to Company Name if available. No medical help, diagnosis, or advice should be withheld from the Participant due to an inability to contact Company Name.

8.7 Expeditable Events (SUSAR’s)

Expeditable events are those adverse events that are CAUSALLY related to the study product, AND that are both SERIOUS (see Section 8.2) and UNEXPECTED (see Section 8.8.3). Such events are subject to expedited reporting to regulatory authorities and will be reported within the stipulated timelines by (Company Name Ltd Pty) or a suitably qualified designee.
8.8 Evaluating AEs and SAEs

8.8.1 Assessment of Intensity

The investigator will make an assessment of intensity for each AE and SAE reported during the study. The assessment will be based on the investigator’s clinical judgement. The intensity of each AE and SAE recorded in the CRF should be assigned to one of the following categories:

**Mild**: An event that is easily tolerated by the Participant, causing minimal discomfort and not interfering with everyday activities.

**Moderate**: An event that is sufficiently discomforting to interfere with normal everyday activities.

**Severe**: An event which is incapacitating and prevents normal everyday activities.

An AE that is assessed as severe should not be confused with an SAE. Severity is a category utilised for rating the intensity of an event; and both AEs and SAEs can be assessed as severe. An event is defined as “serious” when it meets one of the pre-defined outcomes as described in Section 8.2 “Definition of an SAE”.

8.8.2 Assessment of Causality

The investigator is obligated to assess the relationship between investigational product and the occurrence of each AE/SAE. The investigator will use clinical judgment to determine the relationship. Alternative causes, such as natural history of the underlying diseases, concomitant therapy, other risk factors, and the temporal relationship of the event to the investigational product will be considered and investigated. The investigator will also consult the CIB and/or product information in the determination of his/her assessment.

The causal relationship to the study product assessed by the Investigator (or medically qualified delegate) should be assessed using the following classifications:

**Not Related**  In the Investigator’s opinion, there is not a causal relationship between the study product and the adverse event.

**Unlikely**  The temporal association between the adverse event and study product is such that the study product is not likely to have any reasonable association with the adverse event.

**Possible**  The adverse event could have been caused by the study Participant’s clinical state or the study product.

**Probable**  The adverse event follows a reasonable temporal sequence from the time of study product administration, abates upon discontinuation of the study product.
product and cannot be reasonably explained by the known characteristics of the study Participant’s clinical state.

**Definitely**
The adverse event follows a reasonable temporal sequence from the time of study product administration or reappears when study product is reintroduced.

There may be situations when an SAE has occurred and the investigator has minimal information to include in the initial report to Company Name. However, it is very important that the investigator always makes an assessment of causality for every event prior to transmission of the SAE form to Company Name. The investigator may change his/her opinion of causality in light of follow-up information, amending the SAE form accordingly. The causality assessment is one of the criteria used when determining regulatory reporting requirements.

### 8.8.3 Assessment of Expectedness

**Expected**
An adverse reaction, the nature or severity of which is consistent with the applicable product information (e.g. Investigators’ Brochure) for an unapproved medicinal product.

**Unexpected**
An adverse reaction, the nature or severity of which is not consistent with information in the relevant source document (e.g. Investigators’ Brochure for an unapproved medicinal product).

### 8.9 Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each Participant and provide further information to Company Name on the Participant’s condition.

All AEs and SAEs documented at a previous visit/contact and are designated as ongoing, will be reviewed at subsequent visits/contacts.

All AEs and SAEs will be followed until resolution, until the condition stabilises, until the event is otherwise explained, or until the Participant is lost to follow-up. Once resolved, the appropriate AE/SAE CRF page(s) will be updated. The investigator will ensure that follow-up includes any supplemental investigations as may be indicated to elucidate the nature and/or causality of the AE or SAE. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.

New or updated information will be recorded on the originally completed SAE form, with all changes signed and dated by the investigator. The updated SAE form should be resent to Company Name.
8.10 Post-study AEs and SAEs

A post-study AE/SAE is defined as any event that occurs outside the AE/SAE detection period as defined in Section 8.4 “Time Period, Frequency, and Method of Detecting AEs and SAEs” of the protocol.

Investigators are not obligated to actively seek AEs or SAEs in former study participants. However, if the investigator learns of any SAE, including death, at any time after a Participant has been discharged from the study, and he/she considers the event reasonably related to the investigational product, the investigator will promptly notify Company Name.
9 Participant Completion and Discontinuation

9.1 Participant Completion

9.2 Stopping Rules / Discontinuation Criteria

The details and justification of any stopping rules or discontinuation criteria should be provided.

9.3 Participant Withdrawal

Participant withdrawal criteria should be provided, and withdrawal procedures outlined. This should include: When and how to withdraw participants; the type and timing of data to be collected; whether and how participants are to be replaced; the follow up process for withdrawn participants.

9.4 Early Termination of the Study

The study may be terminated prematurely by the principal investigator or his/her designee and the sponsor if:

- The number and/or severity of adverse events justify discontinuation of the study
- New data become available which raise concern about the safety of the study drug, so that continuation might cause unacceptable risks to participants.

In addition (Company Name) reserves the right to discontinue the trial prior to inclusion of the intended number of participants, but intends only to exercise this right for valid scientific or administrative reasons.

After such a decision, the Investigator must contact all participating participants within two weeks, and written notification must be sent to the Reviewing Ethics Committee and relevant Governance Offices.

10 Case Report Form (CRF)

A Case Report Form (CRF) will be completed for each study Participant summarising all clinical screening and study data. Participants will only be referred to in the CRF by their Participant number and initials in order to retain Participant confidentiality.

The completed original CRF’s are to be sent to the Sponsor as soon as practical after completion and review. A copy of each completed CRF is to be retained by the Investigator for a period of time as determined by local regulations.

The identification of data to be recorded directly in to the CRF (i.e. no prior written or electronic record of data), and to be considered to be source data, is outlined in the Source Document Designation Form.
11 Data Analysis and Statistical Considerations

11.1 Hypotheses

If applicable.

11.2 Endpoints

Details of all efficacy/safety endpoints should be provided as applicable. If appropriate, these should be split into primary and secondary.

11.3 Sample Size

The following should be considered and included in this section: Number of participants planned to be enrolled - in multicentre trials, the numbers of enrolled participants projected for each trial site should be specified; The reason for choice of samples size, including reflections on (or calculations of) the power of the trial and level of significance with clinical justification; And the selection of participants to be included in the analyses (e.g. all randomised participants, all dosed participants, all eligible participants, evaluable participants etc).

11.4 Statistical Analysis

A description of all statistical methods to be employed, including timing of any planned interim analysis(ses) should be outlined. Procedures for accounting for missing, unused, and spurious data and reporting any deviation(s) from the original statistical plan should be described and justified.

11.5 Additional Analyses

Any additional analyses should be outlined as appropriate.

12 Data Management

An outline of the data management process should be outlined, to include: Where the analysis will take place; how data will be entered on the database; how data will be tracked, checked and audited; And which SOPs are to be followed.

13 Monitoring and Quality Assurance

The task of the Study Monitor is to guarantee the best conduct of the study through frequent contacts by phone and in person with the responsible Investigator, in accordance with the Monitor’s Standard Operating Procedures, with the purpose of facilitating the work and fulfilling the objectives of the study. These site visits will enable the Monitor to maintain current, personal knowledge of the study through review of the records, comparison with source documents, and observation and discussion of the conduct of the study with the Investigator. The Monitor is responsible for monitoring
adherence to the Protocol and completion of the CRF, and for the relationship between the Investigator and Company Name.

The organisation, monitoring, supply of study materials and quality assurance of the present clinical study is the responsibility of Company Name or its designee.

In order to ensure the accuracy of data, direct access to source documents by the representatives of both the Study Monitor and regulatory authorities is mandatory. Anonymity of the Participant will be maintained at all times. Company Name reserves the right to terminate the study for refusal of the Investigator/Institution to supply source documentation of work performed in the study.

The investigator is required to submit to the Reviewing HREC, annual (or more frequent if requested) reports of the study.

13.1 Curriculum Vitae and Other Documentation

The present investigation may constitute a part of a national registration file. In order to comply with regulatory requirements in some countries, all Investigators signing the Protocol and all trial staff should provide a current, signed and dated Curriculum Vitae (CV) to be filed by Company Name. The CV should include name, title, occupation, education, research experience and present and former positions. A Staff Signature List is required.

14 Investigator Responsibility

Except where the Principal Investigator's signature is specifically required, it is understood that the term ‘Investigator’ as used in this Protocol and on the CRFs refers to the Principal Investigator or an appropriately qualified member of the staff that the Principal Investigator designates to perform specified duties of the Protocol. The Principal Investigator is ultimately responsible for the conduct of all aspects of the study.

Each Investigator will comply with the local regulations regarding clinical trials and the Investigator responsibilities outlined in the ICH GCP guidelines\[1\].

15 Study Report

An outline of the process of preparing, reviewing, audit and approval of the study report should be provided, including the name of the designated contractor if identified / appropriate.

16 Administrative Procedures

16.1 Ethical Considerations

Information on side effects of the test and reference formulations is summarised in the Investigator's Brochure. The monitoring and safety guidelines are outlined in the Monitoring Guidelines for the study. The amount of blood to be sampled in the study is...
not considered to be excessive in healthy adult participants. This study will be carried out according to the Declaration of Helsinki, the NHMRC National Statement on Ethical Conduct in Research Involving Humans (1999) and the Notes for Guidance on Good Clinical Practice as adopted by the Australian Therapeutic Goods Administration (2000) (CPMP/ICH/135/95) and the ICH GCP Guidelines[1].

16.2 Ethical Review Committee

The Protocol will be submitted for approval to the Reviewing Ethics Committee, and written approval obtained from both the HREC and Governance Office, before volunteers are recruited and participants are enrolled. The Investigators will receive all the documentation needed for submitting the present Protocol to the Ethics Committee and/or Governance Office. A copy of the respective approval letters will be transmitted to the Study Monitor before starting the study. The composition of the Ethics Committee must also be provided to the Study Monitor. If approval is suspended or terminated by the Reviewing Ethics Committee or Governance Office, the Investigator will notify the Study Monitor immediately.

It is the responsibility of the Investigator to report study progress to the Reviewing Ethics Committee or Governance Office as required or at intervals not greater than one year.

The Principal Investigator, or his/her nominee, will be responsible for reporting any serious adverse events to the Reviewing Ethics Committee and site governance Office as soon as possible, and in accordance with the guidelines of the State Guidelines.

16.3 Regulatory Authorities

An outline of the process for appropriate regulatory approval should be provided. For example, whether an IND will be submitted for FDA approval of the study (for studies to be conducted/submitted within the USA), or whether the Clinical Trial Notification (CTN) requirements of the Therapeutic Goods Administration (TGA) will be met (for studies to be conducted within Australia) etc.

Any specific requirements of the regulatory authorities, such as reporting of Serious Adverse Experiences (SAEs) should also be outlined.

In agreeing to the provisions of the Protocol, these responsibilities are accepted by the Investigator.

16.4 Informed Consent

Before recruitment and enrolment into the study, each prospective candidate will be given a full explanation of the nature and purposes of the study, and a copy of the Participant Information Sheet to review. Once the essential study information has been provided, and the Investigator is assured that each individual volunteer understands the implications of participating in the study, the participants will be asked to give consent to participate in the study by signing the informed consent form. The consent forms shall be signed and dated by the appropriate parties. A notation that written informed consent
has been obtained will be made on the participant’s CRF. The completed consent forms will be retained by the Investigator and a copy of these will be provided by the Investigator to the participant.

16.5 Participant Reimbursement

If applicable.

Participants may be reimbursed for out of pocket expenses, inconvenience and time involved. If the study is terminated by (Company Name) or the Investigator(s) prior to completion, or a participant withdraws or is withdrawn from the study before completion, a pro-rata payment will be made at the discretion of the Investigator(s). Reserve participants will also be reimbursed for inconvenience and time involved.

16.6 Emergency Contact with Investigators

All participants will be provided with a Participant Emergency Contact Card with contact details of whom to contact in the case of an emergency.

16.7 Notification of Primary Care Physician

With the consent of the participant, it is the Investigator’s responsibility to notify the primary care physician of the participants’ involvement in the study, provided that such a physician can be identified for the participant. A letter will be sent to the physician stating the nature of the study, treatments, expected benefits or adverse events and concomitant drugs to be avoided. A copy shall be retained by the study site for verification by the Study Monitor.

16.8 Investigator Indemnification

The study is being conducted subject to the ‘Guidelines for Compensation for Injury Resulting from Participation in a Company-sponsored Clinical Trial’ published by the Medicines Australia. Company Name will reimburse participants for costs of medical care that occur as a result of complications directly related to participation in this study.

16.9 Financial Aspects

The conduct of the study is subject to a Financial Agreement between Company Name and the Investigator or Institution.

16.10 Protocol Amendments

Neither the Investigator nor (Company Name) will modify the Protocol without first obtaining the concurrence of the other in writing. Protocol modifications that impact on participant safety or the validity of the study will be approved by the Ethics Committee.

No changes (amendments) to the Protocol may be implemented without prior approval from the Sponsor and the Reviewing Ethics Committee. If a Protocol amendment
requires changes to the Informed Consent Form, the revised Informed Consent Form, prepared by the Investigator, must be approved by the Reviewing Ethics Committee and site governance officers.

Once the final Protocol has been issued and signed by the Investigator and the authorised signatories, it shall not be informally altered. Protocol amendments are alterations to a legal document and have the same legal status. Therefore, they must pass through appropriate steps before being implemented. In general, any important change that theoretically increases risk to participants constitutes an amendment. Minor changes are administrative changes and need documentation without approval.

It is the responsibility of the Investigator to submit the amendment to the Reviewing Ethics Committee for their approval; written approval should be obtained and a copy provided to the Sponsor. The Sponsor is responsible for determining whether or not the local regulatory authority must be notified of the Protocol change. Completed and signed Protocol amendments will be circulated to all those who were on the circulation list for the original Protocol.

The original signed copy of amendments will be kept in the Study File with the original Protocol. It should be noted that where an amendment to the Protocol substantially alters the study design or the potential risks to the participants, each participant’s consent to continue participation should be obtained.

16.11 Protocol Compliance

The instructions and procedures specified in this Protocol require diligent attention to their execution. Should there be questions or consideration of deviation from the Protocol, clarification will be sought from the Study Monitor. Any participant treated in a manner that deviates from the Protocol, or who is admitted into the study but is not qualified according to the Protocol as amended by Company Name and the Investigator, may be ineligible for analysis and thereby compromise the study.

Only when an emergency occurs that requires a departure from the Protocol for an individual will there be such a departure. The nature and reasons for the Protocol violation/deviation shall be recorded in the CRF and the investigator should notify the sponsor and Reviewing HREC and/or Governance Office as soon as possible.

The Investigator and designees will comply with all applicable federal, state and local laws.

16.12 Archives: Retention of Study Records

All source documents, CRFs and trial documentation will be kept by the Investigator for the appropriate retention period as stipulated by local regulations and ICH-GCP[1].
16.13 Archives: Retention of Other Study Specific Samples

Details should be provided for retention of other study specific samples, such as plasma samples or biopsy samples etc.
17 References

1. Note for Guidance on Good Clinical Practice (CPMP/GCP/135/95) and Note for Guidance on Good Clinical Practice (CPMP/GCP/135/95) annotated with Therapeutic Goods Administration (TGA) comments (DSEB, July 2000)

Full references should be added in the order that they appear in the protocol
Appendix 2 – Study Schedule of Event

A study schema should be added to provide an easy quick reference to all study timings and procedures
Appendix 2

INSERT COMPANY LOGO

CLINICAL INVESTIGATOR’S BROCHURE

Investigational product:
Research name/number:
INN name:
Indication:

Sponsor

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Fax:
Email:

Edition:
Release Date:

This document supersedes Edition number: X.0 dated:

CONFIDENTIALITY STATEMENT

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CONFIDENTIAL

SPONSOR STATEMENT

This Clinical Investigator’s Brochure (CIB) was subject to critical review and has been approved by the following persons:

_________________________   ____________________
Signature      Date

Name:
Add position (medical)
Company

_________________________   ____________________
Signature      Date

Name
Add position (Scientific)
Company
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<th>Description</th>
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</table>
1 Summary

1.1 Background

Disease aetiology and available treatments

1.2 Overview of investigational product

What is it?

What's it do?

How's it work?

Administered how/

Similarity to other compounds

1.3 Chemistry, Manufacturing and Controls

The IP has been manufactured in accordance with Good Laboratory Practice (GLP) and Good Manufacturing Practice (GMP) for toxicological and clinical studies respectively.

The IP is produced utilising a process involving

1.4 Nonclinical Studies

1.4.1 Pharmacology

There are no fully validated animal models for XXXX. No in vivo assessment of the efficacy of IP has been conducted.

1.4.2 Pharmacokinetics

Pharmacokinetic studies were conducted in

1.4.3 Toxicology

1.5 Clinical Experience

As of the date of this Investigator's Brochure, the IP has not been administered to humans.

1.6 Development plan

Initial Phase I investigations in healthy volunteers will be used to assess the safety and tolerability of IP when administered weekly up to doses of XX mg/kg. Data derived from preliminary pharmacokinetic information will be used to design a subsequent Phase Ib study .....
2 Introduction

Overview of targeted disease and indication

2.1 Investigational product

2.2 Rationale for clinical development

2.3 Dose justification

Table 2-1: Safety ratios for single oral doses

<table>
<thead>
<tr>
<th>Human Single Dose</th>
<th>Rat NOAEL XX mg/kg/day</th>
<th>Dog NOAEL XXX mg/kg/day</th>
</tr>
</thead>
<tbody>
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</tbody>
</table>
3 Physical, Chemical and Pharmaceutical Properties AND Formulation

Drug substance

The active pharmaceutical ingredient is API is structurally similar to (add info)

Table 3-1: Composition and characteristics of active ingredient

<table>
<thead>
<tr>
<th>NAME</th>
<th></th>
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</thead>
<tbody>
<tr>
<td>INTERNATIONAL NOMENCLATURE</td>
<td></td>
</tr>
<tr>
<td>SPONSOR NAME</td>
<td></td>
</tr>
<tr>
<td>CAS NUMBER</td>
<td></td>
</tr>
<tr>
<td>STRUCTURE</td>
<td></td>
</tr>
<tr>
<td>MOLECULAR FORMULA</td>
<td></td>
</tr>
<tr>
<td>MOLECULAR WEIGHT</td>
<td></td>
</tr>
<tr>
<td>DESCRIPTION</td>
<td>EXAMPLE: IP IS A SYNTHETIC XXXX. THE ACTIVE IS PRODUCED IN A SINGLE STEP FROM XXX WITH A PURITY TYPICALLY GREATER THAN 99%.</td>
</tr>
<tr>
<td>ODOR</td>
<td>IP IS A WHITE TO OFF-WHITE CRYSTALLINE XXXX SALT WITH A PKA OF XX. THE MELTING POINT IS AROUND XX°C. THE ACTIVE HAS A WATER SOLUBILITY OF XX MG/ML (AT PH XX).</td>
</tr>
<tr>
<td>SOLUBILITY</td>
<td></td>
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<tr>
<td>PROPERTIES</td>
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</table>
3.1.1 Manufacture

The active pharmaceutical ingredient XXX, is manufactured and purified through a series of proprietary processing steps which have been validated and performed in accordance with GLP/GMP under license at:

State name and address of manufacturer.

3.1.2 Analysis and characterisation of IP

The identity of IP is confirmed by HPLC and MS with a retention time of XXmin in chromatograms etc.
Purity is confirmed by XXX and analytical assay. Impurities are assessed by …

3.1.3 Stability

3.2 Investigational product

3.2.1 Formulation

The clinical product is formulated in combination with the ingredients shown in Table 3-1 using a series of proprietary processing steps prior to sterilisation by XXX and dispensing into XXXX. IP is formulated to contain XX% active pharmaceutical ingredient.

Table 3-2: General investigational drug product Information

<table>
<thead>
<tr>
<th>INGREDIENT</th>
<th>SPECIFICATION</th>
<th>PURPOSE</th>
<th>CONC (MG/ML)</th>
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<tbody>
<tr>
<td>ACTIVE</td>
<td>BP/USP??</td>
<td>ACTIVE</td>
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<td>EXCIPIENT</td>
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<tr>
<td>SOLUTE</td>
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<td>SOLVENT</td>
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</table>

3.2.2 Manufacturer

3.2.3 Final dosage form and presentation

The IP is supplied in a 5mL glass vial and is formulated at XX% of API and stored at RT.
3.2.4 Posology

Information on exact dose and dosing regimen is provided in the applicable approved study protocol.

3.2.5 Container and packaging

5 mL glass vials are packaged in cartons of 5 ....and shipped under ambient conditions to the clinical trial site.

3.2.6 Storage and handling

The vials are to be stored at RT [15°C–30°C (59°F–86°F)], protected from light in a secure area with limited access to appropriate pharmacists or study personnel.

3.2.7 Stability

Current stability information utilising the GMP material has demonstrated that the IP is stable at RT for up to 12 months.

The stability program is currently ongoing.

3.3 Development pharmaceutics

If required
4 Non-clinical studies

Nonclinical Pharmacology

4.1.1 Summary

4.1.2 In vitro Pharmacology

4.1.2.1 Individual study summaries

4.1.3 In vivo Pharmacology

4.1.3.1 Individual study summaries

Animal models for XXX have not been validated for the prediction of XXXX efficacy in humans. In vivo studies to assess efficacy of XXX in XXX have not been conducted to date.

4.1.4 Mechanism of action

Brief overview…

Further information regarding the mechanism of action is provided in Section XX.

4.2 Pharmacokinetics and Product Metabolism in Animals

4.2.1 Summary

Nonclinical pharmacokinetic studies have characterised basic pharmacokinetic parameters in mice, rats and beagle dogs after single IV dose administration of IP.

4.2.2 Method of Analysis

4.2.3 Single-dose Absorption, Distribution, Metabolism and Excretion

Table 4-1: Mean plasma pharmacokinetic parameters for IP after single-dose administration

<table>
<thead>
<tr>
<th>Species</th>
<th>Ref</th>
<th>Dose (mg/kg)</th>
<th>Route</th>
<th>AUC$_{\text{inf}}$ (μg.h/mL)</th>
<th>C$_{\text{max}}$ (μg/mL)</th>
<th>CL (mL/kg/min)</th>
<th>V$_{ss}$ (L/kg)</th>
<th>T$_{1/2}$ (h)</th>
<th>F%</th>
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<tr>
<td>Mouse</td>
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<td>Rat</td>
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</table>
4.2.3.1 Individual study summaries

4.2.3.2 Absorption

4.2.3.3 Distribution

4.2.3.4 Metabolism

4.2.3.5 Excretion

4.2.4 Multiple-dose Absorption, Distribution, Metabolism and Elimination

4.2.4.1 Individual study summaries

4.2.5 Drug interactions
**Table 4-2: Summary table of Pharmacology studies**

<table>
<thead>
<tr>
<th>Study number /Title</th>
<th>GLP</th>
<th>Species/strain</th>
<th>No/sex/group</th>
<th>Formulation</th>
<th>Dose/Regimen</th>
<th>Route of admin.</th>
<th>Duration</th>
<th>Results</th>
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</table>
4.3  Toxicology and safety studies

4.3.1  Summary

4.3.2  Acute toxicology

4.3.2.1  Individual study summaries

4.3.3  Repeat dose toxicology

4.3.3.1  Individual study summaries

Good to include table of dosing for repeated studies, group, dose, number/sex for main study, TK and PD arms.

4.3.3.2  Toxicokinetic parameters

4.3.3.3  Mortality and clinical observations

4.3.3.4  Clinical pathology and organ weights

4.3.3.5  Histopathological changes

4.3.4  Toxicokinetics

4.3.4.1  Individual study summaries

4.3.5  Chronic toxicology

4.3.5.1  Individual study summaries

No studies on chronic toxicology have been conducted on IP to date. Provide justification such as clinical study design.
4.3.6 Reproductive toxicology

No studies on reproductive toxicity have been conducted on IP to date. Provide justification. Repeat dose testing, discuss results of reproductive organs.

4.3.6.1 Individual study summaries

4.3.7 Safety pharmacology

4.3.7.1 Individual study summaries
**Table 4-3: Summary table of Toxicology studies**

<table>
<thead>
<tr>
<th>Study number /Title</th>
<th>GLP</th>
<th>Species/strain</th>
<th>No/sex/group</th>
<th>Formulation</th>
<th>Dose/Regimen</th>
<th>Route of admin.</th>
<th>Duration</th>
<th>Results</th>
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</table>
4.3.8 Genotoxicity (Mutagenicity)

4.3.8.1 Individual study summaries

4.3.9 Carcinogenicity

4.3.9.1 Individual study summaries

No studies on carcinogenicity have been conducted on IP to date. Provide justification.

4.3.10 Special studies

4.3.10.1 Individual study summaries
5 Effects in humans

Introduction

5.1 Clinical Development Program

The initial clinical study will be a randomised, double-blind, single dose, dose escalation study to evaluate the safety, tolerability and pharmacokinetics of IP following IV infusion in healthy male volunteers. Doses will start at 100 mg, escalating to 500 mg after evaluation of results from lower dose investigations. Doses will not exceed 500 mg.

Consideration of the data will lead to a safety, tolerability, pharmacokinetic and pharmacodynamic Phase Ib study utilising multiple ascending doses in XXX participants.

5.2 Pharmacokinetics, Pharmacodynamics and Product Metabolism in Humans

Single doses of XX mg IP in healthy participants resulted in linear and near dose-proportional increases in plasma concentrations of IP with increasing dose (mean $C_{\text{max}}$ and AUC values increased XX-fold, respectively, overall). The mean $C_{\text{max}}$ of IP ranged from XX–XX µg/mL, and the mean $AUC_{0-\text{inf}}$ ranged from XX-XX µg·h/mL. The mean $T_{\text{max}}$ was XX–XX hours after dosing, with a mean terminal half-life ($T_{1/2}$) of XX–XX hours. IP was the major component excreted in urine at all dose levels. Approximately XX–XX% (molecular equivalent) of administered IP was recovered in urine as IP, suggesting that at least that percentage of IP is absorbed.

Table 5-1: Pharmacokinetic parameters of IP following single-dose administration in study no.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>200 mg (n=6)</th>
<th>500 mg (n=6)</th>
<th>1000 mg (n=6)</th>
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</thead>
<tbody>
<tr>
<td>$C_{\text{max}}$ (µg·h/mL)</td>
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<tr>
<td>$T_{\text{max}}$ (h)</td>
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<tr>
<td>$T_{1/2}$ (h)</td>
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<tr>
<td>$AUC_{0-24}$ (µg·h/mL)</td>
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<tr>
<td>$AUC_{0-\text{inf}}$ (µg·h/mL)</td>
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<tr>
<td>CL (L/h)</td>
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</tbody>
</table>

Date: ; Version:
5.3  Clinical experience

5.3.1  Dose response

5.3.2  Safety and Efficacy

5.3.3  Laboratory data and other safety parameters

5.3.4 Individual study summaries

   5.3.4.1 Study no.

   5.3.4.2 Study no. (ongoing)

5.3.5 Benefit – Risk Assessment

5.4  Registration and Marketing experience

To date, IP has not been registered for use or marketed in any jurisdiction.
6 Summary of data and guidance for the investigator

Composition

6.1 Presentation

IP is presented in 10 mL vials for reconstitution prior to administration.

6.2 Posology and route of administration

6.3 Storage and stability

6.4 Pharmacokinetics of investigational product

6.5 Bioanalytical evaluation

6.6 Mitigation of overdose risk

6.7 Expedited Safety Reports

6.8 Warnings, precautions

Insufficient experience exists with IP to provide comprehensive warning guidance. The pharmacokinetics of IP is currently unknown. The investigational product will be administered at a dose of XXXmg etc. Some brief information on putative drug-drug interactions as related to dosing with similar class of compound and potential CYT inhibition criteria.

6.9 Contraindications

IP is contraindicated for use in participants with known hypersensitivity to the active substance or any of the excipients.

6.10 Adverse events

6.11 Participant populations

The investigational compound XXXXX must only be administered in accordance with the approved study protocol inclusion/exclusion criteria.

6.11.1 Pregnancy and Breast-Feeding

No studies of IP in pregnant or lactating women have been conducted. Pregnant and nursing women should not receive IP until further information becomes available. Women of childbearing potential are excluded from participating in IP clinical studies. Sexually active men must use contraception and inform their partners of the possible risks described in this document where and if applicable.

6.11.2 Paediatric Use

No studies on the use of IP in paediatric participants have been conducted.
6.11.3 Geriatric Use

No studies on the use of IP in geriatric participants have been conducted.

References