





# **TABLE OF CONTENTS**

1.	FORWARD	3
2.	ABBREVIATIONS	3
3.	INTRODUCTION	3
3.1	Scope of the SOP Project and why it was developed	4
3.2	What is Good Clinical Practice (GCP)	4
3.3	How these SOPs fit into an overall structure of a Quality System?	5
3.4	Why is GCP relevant to all Australian Researchers?	5
3.5	Consequences of Not Operating to GCP	6
3.6 <b>4.</b>	The Privacy Act and applicability to clinical research WHAT IS A STANDARD OPERATING PROCEDURE?	7 <b>7</b>
5.	THE VMIA GCP STANDARD OPERATING PROCEDURES	8
6.	OVERVIEW OF CONDUCTING CLINICAL TRIALS	9
6.1	Assess whether site is qualified to conduct the trial – Site feasibility	g
6.2	Determine Roles & Responsibilities, Finalise the Study Protocol and Investigator's Brochure	g
6.3	Prepare the Study Site Master File	10
6.4	Prepare the Ethics Submission	10
6.5	Prepare Case Report Forms, Source Documents, Other records and Archiving	10
6.6	Initiate Study/Site and Conduct Study	10
6.7 <b>7.</b>	Close-out activities MONITORING OF STUDIES	10 <b>12</b>
8.	AUDITING OF STUDIES	12
9.	THE VMIA STANDARD OPERATING PROCEDURES - INDEX	13
10.	USEFUL REFERENCE SITES	13
11.	GLOSSARY OF TERMS	14
12.	THE AUSTRALIAN CLINICAL TRIALS REGISTER	18



# 1. Forward

This set of 13 SOPs has been developed to assist the Victorian Public Healthcare Services to operate to at least minimum GCP requirements when conducting clinical trials.

The 13 SOPs are intended to complement and augment, rather than replace, current SOPs that your institute may have in place. These 13 SOPs should be used as a guide only and be adapted, adopted and version controlled by the HREC Office (or Quality Management department) of the institute to ensure, where possible, standard application across your entire organization.

The 13 SOPs have been developed in conjunction with Nucleus Network with the input from both Victorian Public Health Services and pharmaceutical companies. They have been designed to be used by Victorian Public Health Services.

# 2. Abbreviations

ACTR	Australian Clinical Trials Register
AHEC	Australian Health Ethics Committee
CRO	Contract Research Organisation
CTN	Clinical Trial Notification
CRF	Case Report Form
FDA	Food and Drug Administration (USA)
ICH	International Conference on Harmonisation
ICMJE	International Committee of Medical Journal Editor's
NH&MRC	National Health & Medical Research Council
SOP	Standard Operating Procedure
TGA	Therapeutic Goods Administration
VMIA	Victorian Managed Insurance Authority

# 3. Introduction

The Victorian Managed Insurance Authority (VMIA) "The Authority" has a key role in the Clinical Research industry in Victoria. The Authority insures all public hospitals across the State and is involved in the process of obtaining ethics approval in order to initiate clinical research through the insured institutions.

The Standard Operating Procedure (SOP) project has been sponsored by VMIA as part of it's risk mitigation for clinical research activity at VMIA insured sites. The key deliverable of the project is the generation of generic SOPs as tools available to meet the regulatory requirements under the *Therapeutic Goods Act 1989*, *Therapeutic Goods Regulations 1989* and *National Health and Medical Research Council Act 1992 and the Therapeutic Goods (Medical Devices) Regulations (2002)*. The Australian Regulatory Authority Therapeutic Goods Administration (TGA) has adopted the Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95) in principle, annotated with comments <sup>1,2</sup>. ICH is an internationally accepted standard for the designing, conducting, recording and reporting of clinical trials. Current legislation requires all studies to be conducted in accordance with the guidelines. This document should be read in conjunction with current legislation, regulations and guidelines as outlined in Section 5.

Clinical Research that is not conducted in accordance with Australian regulatory requirements presents an exposure risk to the VMIA, the site and clinical trial subject. That is, any claim made by a subject in a research study would have recourse against the insurer where the research was not conducted according to Australian law.

<sup>&</sup>lt;sup>1</sup> Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95) – Annotated with TGA comments DSEB July 2000.

<sup>&</sup>lt;sup>2</sup> National Statement on Ethical Conduct in Human Research, National Health and Medical Research Council (2007).



VMIA supports the excellent work conducted by the Victorian (and Australian) clinical research industry aiming to facilitate and support continued growth of the Clinical Research industry while balancing this with appropriate management of risk.

The investigator site SOPs described herein, have been developed by Nucleus Network in collaboration with experts in the clinical research industry each representing various stakeholder groups in the Industry including, pharmaceutical and biotech companies, Contract Research Organisations (CRO) and investigator sites. Nucleus Network is a not-for-profit organisation based in Melbourne that operates four lines of business:

- it conducts clinical trials in its own dedicated facility and coordinates multi-centre studies across various sites
- 2. it provides consulting advice to Australian and International companies on medical product development and regulation
- 3. it teaches Good Clinical Practice (GCP) to investigational sites and associated organisations and conducts globally recognised certification in GCP
- 4. it creates and promotes platforms for enhancement of and growth of the Clinical Research market in Victoria and Australia

# 3.1 Scope of the SOP Project and why it was developed

The SOPs provide a basic framework for Australian/Victorian Investigator sites/Institutions to comply with the principles of Good Clinical Practice as required by the Australian regulators the Therapeutic Goods Administration and the National Health and Medical Research Council (NH&MRC) at clinical research sites. The SOPs are not intended to replace legislation or published guidances including the National Statement and must be compliant with the regulatory framework of the clinical research industry. The SOPs are intended to be adapted to suit local site and ethics committee requirements while still complying with the regulated clinical research industry. Once implemented at the site, the SOPs will provide a basic operational documentation system that should be version controlled and reviewed at regular intervals (nominally every two years) for current applicability. The development of Standard Operating Procedures provide a procedural framework for institutions conducting clinical research consistent with the global expectation of stakeholders in the Industry. These SOPs do not provide an all inclusive list of requirements to conduct clinical research. Site-specific implementation of GCP is required to comply with regulations but the actual processes can vary from site to site.

Clinical studies that are conducted on behalf of the Pharmaceutical Industry may have requirements in addition to those outlined in this SOP series. The additional requirements are usually due to commitments or regulations required to be followed by other regulatory jurisdictions. The VMIA SOP project does not aim to satisfy additional international requirements.

## 3.2 What is Good Clinical Practice (GCP)

Good Clinical Practice (GCP) is an ethical and scientific quality standard for designing, conducting, recording and reporting trials that involve the participation of human subjects. The TGA has adopted the principles of ICH GCP with flexibility for local requirements. One such allowance is the replacement of ICH-GCP Section 3 *Institutional Review Board/Independent ethics committee (IRB/IEC)* with the National Statement on Ethical Conduct in Research Involving Humans (the National Statement) as published by the National Health & Medical Research Council in 2007. This national ethical standard governs Australia's Human Research Ethics Committees (HRECs) which are responsible for reviewing all research, including clinical research involving humans.

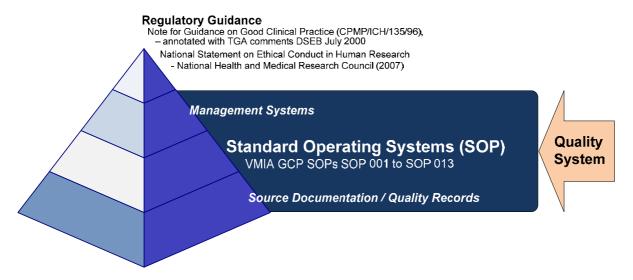
The ICH-GCP guidelines were developed as part of the International Conference on Harmonisation (see Section 10 for website details) which aims to standardise data and product development requirements across the major global regulatory jurisdictions, including "observer" regulatory authorities such as the TGA. As a result, the guideline was intended to be followed when generating clinical trial data intended to be submitted to regulatory authorities. However, as the principles reflected in the guideline are also intended to protect trial participants, acceptance of the principles contained in the guidance document have been extended to other clinical investigations that may impact on the safety and well-being of the subjects.



As a result, it is generally accepted worldwide that the principles of ICH-GCP should be followed whenever conducting clinical research.

The definition of GCP according to the guideline is a "standard for the design, conduct, performance, monitoring, auditing, recording, analyses, and reporting of clinical trials that provides assurance that the data and reported results are credible and accurate, and that the rights, integrity and confidentiality of trial subjects are protected".

#### 3.3 How these SOPs fit into an overall structure of a Quality System?



Together with the regulatory guidance documents, this set of SOPs provides a starting point to the development of an overriding Investigational Site Quality System. They provide practical guidance and application of the regulatory guidance and statement documents. However, in an effort to assure the quality of clinical research, management systems should also be considered for development and implementation to compliment these SOPs.

## What is a Quality System?

A Quality System or Quality Management System can be defined as a set of policies, processes and standard operating procedures required for planning and execution of clinical research activities. The objective of the quality system is to integrate various internal processes to identify, measure, control and improve the processes that will ultimately lead to the assurance of clinical research participant protection and clinical data integrity.

# What are Management Systems?

Key components of management systems include Clinical Risk Management, Research Governance, OH&S and overall institutional management.

#### The importance of accurate and complete Source Documentation / Quality Records

As part of clinical research activities source documentation and other quality records are generated. The accurate completion of these records provide evidence that Regulatory, Protocol and SOP compliance requirements have been meet.

#### 3.4 Why is GCP relevant to all Australian Researchers?

The *National Statement on Ethical Conduct in Human Research* is the regulatory guideline for the ethical conduct of Clinical Research in Australia<sup>2</sup>. Section 3.3.3 outlines the fundamental regulatory guidance which defines the standard for clinical research in Australia. Within these guidelines:



Researchers should show that:

(d) the research meets the relevant requirements of the CPMP/ICH Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95), ISO14155 Clinical Investigations of Medical Devices, and the TGA

Clinical investigation of medical devices is not strictly governed by ICH-GCP. Devices trials must be conducted in accordance with ISO standard 14155 on the *Clinical Investigation of Medical Devices on human subjects* under the Therapeutic Goods (Medical Devices) Regulations (2002). However, many of the principles of ICH-GCP are also found in the devices regulations and standards.

Within the ICH-GCP guidelines there are a number of requirements on research sites that should be known and understood, these are covered in *ICH GCP section 4 Investigator:* 

- 4.1 Investigator Qualifications and Agreements
- 4.2 Adequate Resources
- 4.3 Medical Care of Trial Subjects
- 4.4 Communication with IRB / IEC
- 4.5 Compliance with protocol
- 4.6 Investigational Products
- 4.7 Randomization Procedures and Unblinding
- 4.8 Informed Consent of Trial Subjects
- 4.9 Records and Reports
- 4.10 Progress reports
- 4.11 Safety Reporting
- 4.12 Premature Termination or Suspension of a Trial

Clinical research sites may also be involved in aspects of the Sponsor's responsibilities such as in the preparation of the trial Protocol and the Investigator's Brochure. Furthermore, sites may also act in the capacity of local sponsor for clinical studies either on behalf of an overseas organisation or as an investigator-initiated clinical study. Sites participating in these activities are therefore subject to the following requirements:

ICH GCP Section 5 Sponsor ICH GCP Section 6 Clinical Trial Protocol and Protocol Amendments ICH GCP Section 7 Investigator's Brochure

All sites are also subject to *ICH GCP Section 8 Essential Documents for the Conduct of a Clinical Trial*. Trial Master Files need to be established at the investigational site and these must contain the multitude of documents as required by this section in addition to supplementary documentation such as file notes and site gueries all of which must be collected and maintained at the site.

#### 3.5 Consequences of Not Operating to GCP

Compliance with the GCP guideline provides assurance that the rights, safety and well-being of trial subjects are protected; consistent with the principles that have their origin in the Declaration of Helsinki, and that the clinical trial data are credible. Non compliance with ICH-GCP may lead to risks to the safety and well-being of the trial subjects or credibility of the clinical trial data being compromised.

Non-compliance to ICH-GCP may be detected by study monitors or auditors or when a safety issue arises requiring investigation by a suitably qualified individual. Non-compliance may lead to a clinical hold or study closure by the Sponsor or worse-case, postponing all further operations when directed by a regulatory authority.

ICH-GCP is regarded as the international base standard for the conduct of clinical research. Many countries have supplemented the basic ICH guidelines with varying levels of additional regulation and guidance. Australia, as mentioned above, through the TGA and NHMRC have added their own additional guidances as well as having adopted those of the European regulators. The United States of America through their regulatory agency, the Food and Drug Administration (FDA), have created a more prescriptive version of ICH principles in the Code of Federal Regulations.



The sharp increase in number of CTN applications over the last 20 years and subsequently, number of clinical trials conducted in Australia under the Clinical Trial Notification Scheme (CTN), has lead to varying degrees of knowledge and subsequent compliance capability with regard to GCP. This variability in adherence to GCP standards has several potential impacts on the institution:

- Patients are potentially put at risk when GCP is not followed, this can be seen in items such as failing to follow an Ethics Committee approved trial protocol in areas such as Inclusion / Exclusion Criteria etc.
- Studies not conducted in accordance with the National Statement contravene the NHMRC Act and can result in *loss of NHMRC funding to individuals or institutions*.
- Commercially sponsored studies are generally monitored and audited by the sponsor breakdowns in GCP are therefore less common but when they occur it may result in *future work is not conducted* at that department and often that institution by the sponsor. This can also result in loss of work to other states or Australia as a whole.
- Studies where a subject makes a claim that have not been conducted to GCP will result *in increased* exposure to the individuals, institution and VMIA.

Public institutions benefit from the volume of trials in the public hospital system as many of the funds generated through these trials are re-invested in upgrading infrastructure, equipment, services and skills. Similarly, the increased research investment in Australia also results in new or advanced medicinal products and devices being made available to the patient community, concomitantly leading to better patient outcomes and healthcare as well as highly skilled staff.

There are many regulations and laws that impact on the conduct of clinical research within Australia and internationally which will not be reiterated in this document.

## 3.6 The Privacy Act and applicability to clinical research

Clinical research must comply with the Health Privacy Principles contained in the Health Record Act 2001 (Vic). The clinical research site must respect a subject's right to privacy protection. The Health Privacy Principles regulate the way personal data is collected, used, disclosed, held and destroyed and must include personal information collected over the phone, through mail, personal contact or over the internet. The site SOPs must ensure Privacy principles have been implemented at the site. Most public institutions already have a privacy policy in place and they should be followed and applied as applicable to the research governance office.

# 4. What is a Standard Operating Procedure?

A Standard Operating Procedure (SOP) is a specific description of how to undertake a particular task. An SOP has a different status to a 'Policy' or a 'Guideline'. In general a 'policy' will give a high level statement of intent for an organisation or institution as a whole and generally does not specify taks or individual responsibilities. A 'guideline' is a document that provides guidance to individuals and may be quite detailed in its content, however guidelines are open to interpretation and may be followed in part where appropriate. Where an SOP is in place within an institution or organisation it would be expected that procedure would be followed as described by all of the relevant people referred to within the procedure.

Failing to follow an SOP would be seen as a breach of process from the point of view of an audit or from the legal perspective. Failing to follow a guideline may be explained by circumstance or other factors.

It is important to understand that implementing the VMIA SOPs at your institution will then imply that these SOPs are then followed as written. Where local requirements need to be added the SOPs should be updated to reflect actual practice at your institution. It should be noted that this set of SOPs has been written to describe <u>minimum</u> requirements. In general it would be expected that where the SOPs are modified, the modification would tighten or expand on requirements rather than reduce the requirement.



# 5. The VMIA GCP Standard Operating Procedures

To assist Victorian public hospital clinical research sites to meet their regulatory and legal requirements, a number of basic Standard Operating Procedures (SOPs) should be in place. A series of generic SOPs have been complied that could be made available to clinical research sites throughout Victoria and/or (Australia). The SOPs are intended to be readily adapted and integrated into site clinical research operations. They are provided as tools to assist with implementing the legislation, regulations and guidelines for conducting clinical research. However, specialist GCP training would lead to a better understanding of their content and intent which would in turn lead to appropriate risk mitigation by the clinical research site.

The SOPs listed below are those of particular relevance to the investigational site and site staff such as investigators, study coordinators, research nurses and physicians. involved in clinical research. The SOPs do not cover the areas of Ethics Committees and broader issues of research ethics and governance as these are more specifically addressed in the *National Statement*.

The SOPs cover the following topics and would be considered the minimum to meet ICH- GCP standards at an investigational site:

SOP Number	Title
VMIA GCP SOP 001	Documentation of Investigational site Qualifications,
	Adequacy of Resources and Training Records
VMIA GCP SOP 002	The Study Site Master File and Essential Documents
VMIA GCP SOP 003	Communication with HREC, Trial Sponsor and Insurer
VMIA GCP SOP 004	Protocol and Investigational Brochure Content, Design,
	Amendments & Compliance
VMIA GCP SOP 005	Receipt and Handling of Investigational Product
VMIA GCP SOP 006	Informed Consent procedures and writing Patient Informed
	Consent Forms
VMIA GCP SOP 007	Case Report Forms, Source Documents, Record keeping
	and Archiving
VMIA GCP SOP 008	Site Initiation and Close-out
VMIA GCP SOP 009	TGA Notification and SAE Reporting Requirements
VMIA GCP SOP 010	Investigator Responsibilities
VMIA GCP SOP 011	Sponsor Responsibilities & Investigator initiated studies
VMIA GCP SOP 012	Handling & Shipping of Infectious Substances for Clinical
	Trials
VMIA GCP SOP 013	Standard Operating Procedure Creation, Implementation
	and Revision

Associated with these procedures are a number of 'Model Documents' forms that can be used as templates for documenting the various requirements contained under ICH guidelines.

The aim of these SOPs is to provide the necessary tools to ensure that Clinical Research sites are able to operate to ICH-GCP standards by efficiently providing operating documentation. It is envisaged that institutions should be able to down-load .doc files from the VMIA website at <a href="www.vmia.gov.au">www.vmia.gov.au</a> so that they can further develop and implement their own procedures from the generic document provided by VMIA.

# How to use these generic SOPs

In many institutions there are a number of Standard Operating Procedures already in place. Where there are already SOPs in place that cover clinical research, research governance or GCP, these should be reviewed against the VMIA SOPs. Institutions may choose to adopt the VMIA SOPs unchanged or they may like to incorporate them into their existing documents. As mentioned previously, the VMIA SOPs represent the minimum requirement to meet GCP obligations.

The SOPs should be managed through the document control system of the of the institution adopting them. Relevant staff should be made aware of the SOPs and the institutional policy regarding adherence to them.



Some training in the VMIA SOPs will be offered via the VMIA seminar series, however it is up to institutional policy to determine and keep written records local training requirements.

The VMIA GCP SOPs are not a complete instruction book for the conduct of clinical trials. There are a number of useful documents that the VMIA recommends be reviewed and be available to clinical research groups within each institution:

- [your own Institutional research governance policies & procedures]
- National Statement on Ethical Conduct in Human Research NHMRC 2007
- Australian Clinical Trial Handbook TGA 2006
- Victorian Managed Insurance Authority Guidelines for Clinical Trials for Victorian Public Hospitals – VMIA 2006
- Note for Guidance on Good Clinical Practice- (CPMP/ICH/135/96) as annotated by the TGA
- Access to Unapproved Therapeutic Goods Clinical Trials in Australia TGA 2004
- Human Research Ethics Committees and the Therapeutic Goods legislation TGA 2001

# 6. Overview of Conducting Clinical Trials

Clinical trials require significant preparation both logistically and from a documentation point of view. Many documents require approvals from ethics committees and Sponsors before the first subject can enter screening and the clinical trial commence. Likewise a significant amount of effort is required during the conduct of the studies through to close-out and adequate archiving of research records records. The flow chart represented in Figure 1 shows the key steps in the conduct of a clinical trial as described below and relates these steps to the VMIA Standard Operating Procedures.

#### 6.1 Assess whether site is qualified to conduct the trial – Site feasibility

According to GCP it is unethical to commence a trial with:

- → inadequate resources to conduct the study to completion
- → insufficient participants to meet the study objectives
- → insufficient experience of the study staff to conduct the trial

Study sites should have documented evidence of adequate training and qualification of staff, identification of resources and review of subject availability. Documentation that may be included in this are:

- → Training files & CVs of staff
- → Clinical Trial Agreements (especially in the case of commercially-sponsored studies)
- → Resource Declarations from hospital departments (used as part of the standard DHS ERC common submission package see <a href="www.health.vic.gov.au/ethics/application/common\_app\_form.htm">www.health.vic.gov.au/ethics/application/common\_app\_form.htm</a>
- → Deidentified listings of subject recruitment and/or reports

#### 6.2 Determine Roles & Responsibilities, Finalise the Study Protocol and Investigator's Brochure

The clinical trial protocol is the key "instruction sheet" for the conduct of the trial. This is the document that is reviewed and approved by an ethics committee to ensure that the research study is ethically acceptable. Study tasks should be conducted in accordance with the protocol and any questions that study staff have should be answered by the protocol or study reference manuals. Where the protocol does not provide an answer a protocol amendment may be required. Protocol deviations should be documented in a "note to file" or in source notes. The reason for the deviation must be provided.

The investigator's brochure is a summary of all of the knowledge about the drug or device that is currently known. The IB is a very important document for unregistered investigational products as it contains the scientific safety information necessary to assess whether the product or device has been tested sufficiently safety studies to be used in humans at the dosage or method described in the protocol.



When considering the conduct of a trial, the roles and responsibilities of the study staff need to be considered. For example, if the protocol requires a cardiologist to review all ECGs, the site must ensure one is available and committed to the study?

## 6.3 Prepare the Study Site Master File

The study Site Master File is a file that contains all key documentation that is required under ICH-GCP. This file is built up progressively during the preparation, conduct and close-out of a clinical trial. The SOP provides a detailed check-list of each of the required documents. The study site Master file is a key document for study auditors or inspectors – these may be from ethics committee, institution, sponsor, Australian regulatory agency (TGA), international regulatory agency (e.g FDA).

## 6.4 Prepare the Ethics Submission

The ethics submission and approval process is a mandatory step in any human research study. Each institutional (or central) ethics committee is constituted in line with the NHMR / AHEC guidelines. The ethics committee is responsible for ensuring research participant protection and that the study design complies with GCP guidelines. Most institutions provide their own guidelines for ethics applications, however the DHS common application checklist or the NEAF (National Ethics Application Form) provide comprehensive checklists of questions and materials to submit in an ethics application.

# 6.5 Prepare Case Report Forms, Source Documents, Other records and Archiving

Research records (notes/data) are recorded in the Case Report Form (CRF), however these records may not be the "source documents". The Source document is the first document used to record the study/source data and subsequently represents the first time a piece of information is recorded during a trial. A source document may be the doctor's notes in the medical record, an x-ray, a pathology result print-out, a patient diary etc. In some studies the data is recorded directly into the CRF, and in this case this may be outlined in the ethics approved protocol such that the CRF therefore becomes the source document. All original source documents and CRFs need to be retained in line with institutional, regulatory authority, GCP and other national requirements (which ever is longer). It is important therefore to organise archiving of documents at the end of the study.

# 6.6 Initiate Study/Site and Conduct Study

An important part of conducting a research study is to 'initiate' the study in a formal way. The initiation of the study makes sure that the site staff are aware of their responsibilities, specific study requirements and study commitments. Staff present at the initiation meeting should be documented in writing as having attended.

The study must be conducted in accordance with the ethics approved protocol and clinical study data captured for all aspects in order to provide full traceability of procedures conducted and decisions made. The end documentation product must allow full reconstruction of the trial by an auditor or regulatory authority and provide easily read audit trails.

#### 6.7 Close-out activities

A clinical trial needs to be formally closed-out to ensure that all of the study activities are completed, when all subjects have completed their study requirements. Documentation of the research must be retained and archived. Archived information must be easily retrieved and available for review by auditors or regulatory authorities.



SOP 013 -

# 1. Site Feasibility

SOP 001 - Site qualifications, resources and training records

SOP 005 - Receipt and handling of investigational product

# 2. Roles, Responsibilities

SOP 004 - Protocol and investigational brochure content, design, amendments and compliance

SOP 011 - Sponsor responsibilities & investigator driven studies

# 3. Ethics Submission

SOP 003-

SOP 006-

SOP 009-

# 4. Site Master File

SOP 003-

5. CRFs, source documents, records and archiving

SOP 007-

# 6. On-Study

SOP 008-

SOP 010-

SOP 012-

SOP 009-

SOP 005-

SOP 001 -

SOP 011 -

SOP 002-

SOP 006-

# 7. Close-out study

SOP 008-



# 7. Monitoring of Studies

According to the *National Statement*, all clinical research projects are required to be monitored by the approving institution (Section 5.5 of National Statement). This is a separate and distinct monitoring function via the institutions Research Governance office and is not to be confused with monitoring by sponsors which is covered in Section 5.18 of ICH-GCP. The frequency and type of monitoring by the institution should be determined by the degree of risk to research participants.

#### **Institutional** monitoring can include:

- Requirements for research reports from investigators
- Requirements from reports from independent agencies (eg. Data Safety Monitoring Board (DSMB))
- Review of Adverse Events
- Random inspections of sites, data, or consent documentation
- Interviews with research participants or other forms of feedback from them

# **Sponsor** monitoring

Clinical Trial Agreements between sponsors and sites will require the sponsor to undertake monitoring of the study. Sponsor monitoring can be quite intense and will generally include verification of research data from the original source documentation and compliance of the site to ICH GCP and local regulatory requirements. Subject consent forms will include a statement allowing sponsors and regulatory agencies to review their data for the purposes of verification. Sponsor monitors may review any or all aspects of the trial and this may include:

- Review of medical records & consent forms
- · Review of site files
- Review of HREC documentation
- Review of equipment & facilities
- Review of policies & procedures

# 8. Auditing of Studies

Clinical studies may also be subject to Audit from a number of sources:

- Institutional Governance Office
- Domestic Regulatory & Government Agencies (e.g. TGA, DHS)
- International Regulatory Agencies (e.g. FDA, EMEA)
- Sponsor companies (e.g. Pharma & Biotech companies)
- Domestic granting bodies (e.g. NHMRC, ARC)
- International granting bodies (e.g. NIH, JDRF)
- Insurers (e.g. VMIA)

Local regulatory agencies, responsible government departments and insurers have either legislative or contractual access to conduct audits. The Clinical Trial Agreement or similar is a contract that is signed by the investigator or institution and this allows access by international agencies, sponsors and granting bodies.

An audit is a thorough examination and verification of the research conduct at the site. An audit may be undertaken as part of routine verification of standards or it may be for a specific reason (these are sometimes referred to as a "for cause audit"). A 'for cause' audit may be triggered through routine monitoring or atypical data, adverse events or suspected fraud.

An audit may be focussed or may cover all aspects of clinical research conduct. Audits are generally significantly more rigorous than monitoring of studies. Audits are also more likely to focus on broader issues such as SOP compliance, training records, staff qualification, facilities, risk management.



# 9. The VMIA Standard Operating Procedures - Index

SOP 001: Documentation of Investigational Site Qualifications, Adequacy of Resources

and Training Records

SOP 002: The Study Site Master File and Essential Documents SOP 003: Communication with HREC, Trial Sponsor and Insurer

SOP 004: Protocol and Investigational Brochure Content,

Design, Amendments & Compliance

**SOP 005:** Receipt and Handling of Investigational Product

SOP 006: Informed Consent procedures and writing Patient Informed Consent Forms
SOP 007: Case Report Forms, Source Documents, Record keeping and Archiving

**SOP 008:** Site Initiation and Close-out

**SOP 009:** TGA Notification and SAE Reporting Requirements

SOP 010: Investigator Responsibilities

**SOP 011:** Sponsor Responsibilities & Investigator initiated studies

**SOP 012:** Handling & Shipping of Infectious Substances for Clinical Trials

**SOP 013:** Standard Operating Procedure Creation, Implementation and Revision

# 10. Useful Reference Sites

# **Ethics Applications**

www.health.vic.gov.au/ethics/application/common\_app\_form.htm

www.neaf.gov.au

www.nhmrc.gov.au/ethics/human/ahec/

## **GCP Guidelines / National Statement**

www.nhmrc.gov.au/ethics/human/ahec/

www.nhmrc.gov.au/publications/synopses/e35syn.htm

www.emea.europa.eu/pdfs/human/ich/013595en.pdf

#### **GCP Training**

www.nucleusnetwork.com.au

# **Regulatory Agencies**

www.tga.gov.au

www.anztpa.gov.au

www.emea.europa.eu/pdfs/human/ich/013595en.pdf

www.fda.gov

www.vmia.vic.gov.au



# 11. Glossary of Terms

#### Adverse device event

A clinical sign, symptom or condition that is causally related to the device implantation procedure, The presence of the device, or the performance of the device system.

#### Adverse drug reaction

Any noxious and unintended response to an unapproved medicinal product, related to any dose. The phrase "response to an unapproved medicinal product" means that a causal relationship between the product and an adverse event is at least a reasonable possibility, i.e. the relationship cannot be ruled out. ('Unapproved medicinal product' here includes approved products used at levels or in ways that are unapproved)

#### or

A noxious and unintended response to a drug that occurs at doses of marketed medical products normally used in humans for prophylaxis, diagnosis or therapy of diseases or for modification of physiological function.

#### Adverse event (device)

Any undesirable clinical occurrence in a subject, whether it is considered to be device-related or not, that includes a clinical sign, symptom or condition and/or an observation of an unintended technical performance or performance outcome of the device.

#### Clinical trial

A form of research designed to find out the effects of an intervention, including a treatment or diagnostic procedure.

# Confidentiality

The obligation of people not to use private information – whether private because of its content or the context of its communication - for any purpose other than that for which it was given to them.

#### **Conflict of interest**

In the research context: where a person's individual interests or responsibilities have the potential to influence the carrying out of his or her institutional role or professional obligations in research;

## or

where an institution's interests or responsibilities have the potential to influence the carrying out of its research obligations.

#### Consent

A person's or group's agreement, based on adequate knowledge and understanding of relevant material, to participate in research.

### Ethical / unethical

Right or morally acceptable / wrong or morally unacceptable.

#### **Ethical review**

Review of research by an HREC or other body.



#### Ethical review body

Body set up to carry out ethical review of human research.

#### **Ethics**

The concepts of right and wrong, justice and injustice, virtue and vice, good and bad, and activities to which these concepts apply.

#### Harm

That which adversely affects the interests or welfare of an individual or a group. Harm includes physical harm, anxiety, pain, psychological disturbance, devaluation of personal worth and social disadvantage.

#### **HREC**

Human Research Ethics Committee.

#### Individually identifiable data

Data from which the identity of a specific individual can reasonably be ascertained.

# Low risk (research)

Research in which the only foreseeable risk is one of discomfort.

#### Monitoring (of research)

The process of verifying that the conduct of research conforms to the approved proposal.

## Negligible risk

Research in which there is no foreseeable risk of harm or discomfort, and any foreseeable risk is of inconvenience only.

#### Non-identifiable data

Data that have never been labelled with individual identifiers or from which identifiers have been permanently removed, and by means of which no specific individual can be identified. A subset of non-identifiable data are those that can be linked with other data so it can be known they are about the same date subject, although the person's identity remains unknown,

# Participant (in research)

Anyone who is the subject of research

#### Personal information

Information by which individuals can be identified.

# Placebo (in research)

A substance not containing an active agent under study, administered to some participants to compare the effects of the active agent administered to other participants.

#### **Privacy**

A domain within which individuals and groups are entitled to be free from the scrutiny of others.



#### **Protocol**

A document that provides the background, rationale and objectives of the research and describes its design, methodology, organisation and the conditions under which it is to be performed and managed.

#### Re-identifiable data

Data from which identifiers have been removed and replaced by a code, but it remains possible to reidentify a specific individual by, for example, using the code or linking different data sets.

#### Research

Includes at least investigation undertaken to gain knowledge and understanding or to train researchers.

#### Research misconduct

Includes fabrication, falsification, plagiarism or deception in proposing, carrying out or reporting the results of research, and failure to declare or manage a serious conflict of interest. Also includes failure to follow research proposals approved by a research ethics committee, particularly where this failure may result in unreasonable risk or harm to humans, other animals or the environment. Also includes the wilful concealment or facilitation of research misconduct by others

#### Risk

The function of the magnitude of a harm and the probability that it will occur.

#### Serious adverse event

Any untoward medical occurrence that:

- results in death:
- is life-threatening (NOTE: The term "life-threatening" refers to an event/reaction in which the patient
- was at risk of death at the time of the event/reaction; it does not refer to an event/reaction which hypothetically might have caused death if it were more severe);
- requires inpatient hospitalisation or prolongation of existing hospitalisation;
- results in persistent or significant disability/incapacity;
- is a congenital anomaly/birth defect;
- 0
- is a medically important event or
- reaction.

## Serious unexpected suspected adverse reaction

A serious adverse event (see definition above) for which there is some degree of probability that the event is an adverse reaction to the administered drug, and the adverse reaction is unexpected.

#### **Sponsor**

An individual, company, institution or organisation that takes responsibility for the initiation, management, and/or financing of research.

# Unexpected adverse drug reaction



An adverse reaction, the nature or severity of which is not consistent with the applicable scientific information (e.g. Investigator's Brochure for an unapproved investigational product or Product Information (PI) document or similar for an approved, marketed product).

Where possible this glossary has been adopted from the *National Statement on Ethical Conduct in Human Research*, 2007 and ICH GCP.



# 12. The Australian Clinical Trials Register

#### What is the ACTR?

The Australian Clinical Trials Registry (ACTR) is a national, online register of clinical trials being undertaken in Australia. The ACTR includes trials from the full spectrum of therapeutic areas of pharmaceuticals, surgical procedures, preventive measures, lifestyle, devices, treatment and rehabilitation strategies and complementary therapies. It has nationwide coverage of all clinical trials involving Australian researchers or Australian participants.

The website location can be found at: http://actr.org.au/Default.aspx.

#### When should studies be registered?

Trials should be registered before enrolment of the first patient.

#### How do I register a trial?

Go to the Register Trial section of the above website and enter the required data. Remember to save and verify your information before submitting your trial for registration. There are information buttons next to each data entry box to help you enter the correct information.

## Key points about the ACTR

- Publicly owned, managed by a not-for-profit organisation
- At this point in time, all data submitted to the ACTR is made publicly available
- Registration is voluntary, but if a registrant chooses to register a trial, certain fields are mandatory
- · Registration is free of charge
- Responsibility for registration lies with the Sponsor, defined by the NHMRC and TGA as "an
  individual, company or institution or organization which takes responsibility for the initiation,
  management and/or financing of a clinical trial". It is the Sponsors responsibility to ensure
  that the information submitted is accurate and up-to-date.

## What studies should be registered?

Any project that prospectively assigns human subjects to intervention and comparison groups to study the cause-and-effect relationship between a medical intervention and a health outcome (ICMJE definition) should be registered. A trial must have at least one prospectively assigned concurrent control or comparison group in order to trigger the ICMJE requirement for registration. In addition, in May 2006 the WHO recommended that all interventional clinical trials should be registered, including early phase uncontrolled trials in patients or healthy volunteers (WHO Recommendation). If in doubt, registration is recommended.

#### What information will be recorded?

The registry will record:

- a trial's objectives
- a trial's main design features
- sample size and statistics
- the treatments under investigation
- the outcomes being assessed
- the principal investigators
- the contact details for specific trial information

The ACTR mandatory data items comply with the minimum dataset requirements of the International Committee of Medical Journal Editors (ICMJE).

# STANDARD OPERATING PROCEDURE

# Title : Documentation of Investigational Site Qualifications, Adequacy of Resources and Training Records

Document ID: 001			
Boodinent B. 601			
Version: <insert as="" local="" management="" per="" quality="" site="" system="" version="" your=""></insert>			
Author: <insert approver="" author="" local="" name="" of="" or=""></insert>			
Author Signature:	Date: <insert date=""></insert>		
Effective Date: <insert date="" department="" procedure="" that="" this=""></insert>	e is effective from in your institution/		
Review Before: <insert be="" date="" of="" procedure="" reviewed="" should="" this="" when=""></insert>			
Department/Institution name: < insert Department/institution name>			
Reviewed and Approved by: <insert name=""></insert>	<insert position="" title=""></insert>		
Signature:	Date: <insert date=""></insert>		
Departmental Head: < insert name>			
Signature:	Date: <insert date=""></insert>		

VMIA SOP No. 001

DOCUMENTATION OF INVESTIGATIONAL SITE QUALIFICATIONS, ADEQUACY OF RESOURCES AND TRAINING RECORDS

Version: 1.0 Dated 17 September 2007

#### STRICTLY CONFIDENTIAL

## 1. AIM

To describe the procedures related to the appropriate documentation of investigational site qualifications and training records as well as the provision of resources to perform research appropriately.

## 2. SCOPE

Applicable to all phases of clinical investigation of medicinal products, devices and diagnostics.

#### 3. APPLICABILITY

Principal Investigator, Sub-Investigator(s), research co-coordinators and other staff involved in trial-related duties.

#### 4. PROCEDURE

# 4.1 Documentation of Investigational Site Qualifications and Training Records

#### The investigator(s) should:

- Maintain an up-to-date *Curriculum vitae* and review on a yearly basis.
- Be qualified by education, training, and experience to assume responsibility for the proper conduct of the trial. This should be evidenced in the CV.
- Meet all the qualifications specified by the applicable regulatory requirement(s). Current medical practitioner registration details and similar documentation should be referenced in the CV.
- Provide evidence of such qualifications through up-to-date *Curriculum vitae* and/or other relevant documentation requested by the sponsor, the HREC, and/or the regulatory authority(ies).
- Maintain a list of appropriately qualified persons to whom the investigator has
  delegated significant trial-related duties. The list is in the form of a Delegation
  Log and delegated duties should be captured and signed and dated by the
  investigator on a per person basis. The delegation log may be provided by the
  Sponsor company but for investigator-initiated studies, a separate site log
  should be developed.

VMIA SOP No. 001

# 4.2 Adequacy of Resources

# The investigator(s) should:

- Be able to demonstrate (if possible based on retrospective data) a potential
  for recruiting the required number of suitable subjects within the agreed
  recruitment period. This may be in the form of de-identified subject
  recruitment listings or other documented written evidence.
- Have sufficient time to properly conduct and complete the trial within the agreed trial period and have available an adequate number of qualified staff and adequate facilities for the foreseen duration of the trial to conduct the trial properly and safely.
- Adequacy of resources are normally determined by a site feasibility assessment for commercially-sponsored studies.
- Many Victorian hospital ethics committees use the DHS common Submission Package form which includes explicit resource declarations (Module 3) from departments involved in the planned study.

# 4.3 Training Records

# The investigator(s) should:

- Ensure that all persons assisting with the trial are adequately informed about the protocol, the investigational product(s), and their trial-related duties and functions. An initiation meeting may be held where all required staff are present and written evidence of study specific training is developed.
- Ensure that documentation of this training be kept current and available for review on request throughout the entire trial period.
- Ensure that tasks delegated to study staff are documented appropriately. This
  can be evidenced by the delegation log. However, study specific training
  records should be maintained to provide evidence that tasks were delegated
  following the correct training.

#### 5. GLOSSARY

# **Good Clinical Practice (GCP)**

A standard for the design, conduct, performance, monitoring, auditing, recording, analyses, and reporting of clinical trials that provides assurance that the data and reported results are credible and accurate, and that the rights, integrity, and confidentiality of trial subjects are protected.

VMIA SOP No. 001

DOCUMENTATION OF INVESTIGATIONAL SITE QUALIFICATIONS, ADEQUACY OF RESOURCES AND TRAINING RECORDS

Version: 1.0 Dated 17 September 2007

#### **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 ensuring 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.

# **Sub Investigator**

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

#### 6. REFERENCES

- 1. Note for guidance on Good Clinical Practice (CPMP/ICH/135/95) annotated with TGA comments DSEB, July 2000.
- 2. National Statement on Ethical Conduct in Human Research, (2007).

# 7. APPENDICES

Appendix 1: SOP Change Log

Appendix 2: Template for Signature and Delegation Log

Appendix 3: Example Training Record Form
Appendix 4: Example Curriculum Vitae Template

#### **DOCUMENT END**

VMIA SOP No. 001

DOCUMENTATION OF INVESTIGATIONAL SITE QUALIFICATIONS, ADEQUACY OF RESOURCES AND TRAINING RECORDS

# **APPENDIX 1: SOP CHANGE LOG**

Version No.	Reason for Issue
1	First issue

VMIA SOP No. 001

DOCUMENTATION OF INVESTIGATIONAL SITE QUALIFICATIONS, ADEQUACY OF RESOURCES AND TRAINING RECORDS

Version: 1.0 Dated 17 September 2007

APPENDIX 2: SIGNATURE LOG AND DELEGATION OF DUTIES (TEMPLATE)

	)IS	GNATURE LOG AN	ND DELE	SIGNATURE LOG AND DELEGATION OF DUTIES (template)	S (templa	ate)	
	Protocol No:						
	Investigator Name:						
	Sponsor:						
Start Date Of Involvement	Print Name	Signature	Sample Initials	Function (e.g. sub-investigator, study nurse)	Task Delegate d	Authorised by Investigator (initial+ date)	End date of Involvement
a. Informed discussion	liscussion		g. Investiga	Investigational product accountability			
b. Informed c	Informed consent sign off		h. Randomi	Randomization of subjects (e.g. IVRS)			
c. CRF/DCF	CRF/DCF Completion and Correction		i. Essential	Essential / Regulatory documents handling			
d. CRF/DCF Sign-Off	Sign-Off		j. Study spo	Study specific procedures			
e. Subject Ex f. Investigation	Subject Examination/evaluation Investigational product dispensation		k. Other				

VMIA SOP No. 001

DOCUMENTATION OF INVESTIGATIONAL SITE QUALIFICATIONS, ADEQUACY OF RESOURCES AND TRAINING RECORDS

Version: 1.0 Dated 17 September 2007

**Document: VMIASOP001 Appendix 3** 

# **Internal Training Record**

Section 1 – Employee (Trainee)	) Details						
Name :		Position	on / Title	:			
section 2 – Training Details							
Date(s) of Training :			Du	ration :			
Type:	Classroom	eLearning [	<u> </u>	Other [	] (Provide detai	ils in Descriptio	n section)
Location :							
Description :							
SOP / Module /Course : (If applicable)						Version :	
Trainer Name :			Title :				
Employee (Trainee) :	Signature or Initials		_		Date	:/	
Trainer Comments (d	describe competency	/ assessment if app	licable)				
Trainer :	Olympia was and Warfe	Titlo			Date	:/_	

[Institution Name] Page 1 of 1

Personal and Current Employment Details		
Name:		
Current Position:		
Start Date to Present:		
Functional Statement:		
	Education – Secondary	
Highest qualification:		
Year:		
Where achieved:		
	Education - Tertiary	
Highest qualification:		
Year:		
Where achieved:		
Highest qualification:		
Year:		
Where achieved:		
Highest qualification:		
Year:		
Where achieved:		
Highest qualification:		
Year:		
Where achieved		
Highest qualification:		
Year:		
Where achieved:		

	Previous Employment History
Employer:	
Start to Finish Dates:	
Position:	
Duties:	
	Previous Employment History
Employer:	
Start to Finish Dates:	
Position:	
Duties:	
	Previous Employment History
Employer:	
Start to Finish Dates:	
Position:	
Duties:	
	Previous Employment History
Employer:	
Start to Finish Dates:	
Position:	
Duties:	
	Previous Employment History
Employer:	
Start to Finish Dates:	
Position:	
Duties:	
	Previous Employment History
Employer:	
Start to Finish Dates:	
Position:	
Duties:	
	Previous Employment History
Employer:	
Start to Finish Dates:	
Position:	
Duties:	

	Lecturers/Associations
Institute:	
Dates	
Topic:	
Institute:	
Dates	
Topic:	
Institute:	
Dates	
Topic:	
	Lecturers/Associations
Institute:	
Dates	
Topic:	
Other	Relevant Education / Training/Activities
Details:	
Year:	
Where undertaken:	
Details:	
Year:	
Where undertaken:	
Details:	
Year:	
Where undertaken:	
Details:	
Year:	
Where undertaken:	

Employee Signature: ...... Date: .....

# STANDARD OPERATING PROCEDURE

Title: The Study Site Master File and	Essential Documents	
Document ID: 002		
Version: <insert as="" local="" per="" quality<="" site="" td="" version="" your=""><td>management system&gt;</td></insert>	management system>	
Author: <insert approver="" author="" local="" name="" of="" or=""></insert>		
Author Signature:	Date: <insert date=""></insert>	
Effective Date: <insert date="" department="" effective="" is="" procedure="" that="" this=""></insert>	ective from in your institution/	
Review Before: <insert be="" date="" of="" procedure="" reviewed="" should="" this="" when=""></insert>		
Department/institution name: < insert Department/institution name>		
Reviewed and Approved by: <insert name=""></insert>	<insert position="" title=""></insert>	
Signature:	Date: <insert date=""></insert>	
Departmental Head: < insert name>		
Signature:	Date: <insert date=""></insert>	

Version: 1.0 Dated 17 September 2007

#### STRICTLY CONFIDENTIAL

### 1. AIM

To describe the procedures related to the maintenance of the study site master file and associated essential documents.

# 2. SCOPE

All phases of clinical investigation for medicinal products, medical devices and diagnostics

#### 3. APPLICABILITY

Principal Investigator/ Investigator, Sub-Investigator(s) research coordinators and other staff involved in trial-related duties.

#### 4. PROCEDURE

# 4.1 The Study Site Master File and Essential Documents

# The investigator(s) should:

- File essential documents at the site in a timely manner. All site-related materials should be made available for review by the sponsor's representatives (monitors and auditors) or regulatory authority(ies).
- Keep a minimum list of essential documents from the following stages of the trial (see Appendix 1).
- Before the clinical phase of the trial
- During the clinical conduct of the trial
- After completion or termination of the trial.
- Study documentation should be maintained for a minimum of 15 years for adult studies or 25 years for paediatric studies.
- For legal reasons, sites may consider indefinite archiving periods.
- The TGA position on document retention states:

"The TGA requires records to be retained by the sponsor for 15 years following the completion of a clinical trial. However, in Australia the overriding consideration for sponsors with respect to record retention is the issue of product liability and the potential need for sponsors of products to produce records at any time during, and possibly beyond, the life of a product in the event of a claim against the sponsor as a result of an adverse outcome associated with the use of the product."

VMIA SOP No. 002

# 4.2 Documentation of Investigational Site Qualifications and Training Records

# The investigator(s) should:

- Maintain an up-to-date Curriculum vitae and review on a yearly basis.
- Be qualified by education, training, and experience to assume responsibility for the proper conduct of the trial. This should be evidenced in the CV.
- Meet all the qualifications specified by the applicable regulatory requirement(s). Current medical practitioner registration details and similar documentation should be referenced in the CV.
- Provide evidence of such qualifications through up-to-date Curriculum vitae and/or other relevant documentation requested by the sponsor, the HREC, and/or the regulatory authority(ies).
- Maintain a list of appropriately qualified persons to whom the investigator has
  delegated significant trial-related duties. The list is in the form of a Delegation
  Log and delegated duties should be captured and signed and dated by the
  investigator on a per person basis. The delegation log may be provided by
  the Sponsor company but for investigator-initiated studies, a separate site log
  should be developed.

#### 4.3 The Site File

- The site file should contain all the essential documentation referred to in Appendix 1.
- For commercially sponsored studies, sponsoring companies will normally provide site file complete with tab separators for ease and consistency of filing.
- For Studies conducted on behalf of smaller companies or for investigatorinitiated studies, the site file should be structured in accordance with the template provided in Appendix 3.
- Financial documentation such as the clinical trial agreement may be filed in a separate location to the Master Site File.
- The site pharmacy will usually keep investigational product shipping, receipt and accountability documents. The site itself does not have to replicate these documents. However, the records must be made available to sponsors monitors and auditors.

#### 5. GLOSSARY

#### **Essential Documents**

Documents which individually and collectively permit evaluation of the conduct of a study and the quality of the data produced

# **Good Clinical Practice (GCP)**

A standard for the design, conduct, performance, monitoring, auditing, recording, analyses, and reporting of clinical trials that provides assurance that the data and reported results are credible and accurate, and that the rights, integrity, and confidentiality of trial subjects are protected.

# **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, 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.

#### **Sub Investigator**

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

## 6. REFERENCES

- Note for guidance on Good Clinical Practice (CPMP/ICH/135/96) annotated with TGA comments DSEB, July 2000
- 2. VMIA CTN Guidelines (2006)

#### STRICTLY CONFIDENTIAL

# 7. APPENDICES

Appendix 1: List of documents to be generated during the conduct of a clinical trial

from initiation to close-out

Appendix 2: SOP Change Log

Appendix 3: Master Site File index and contents template

# **DOCUMENT END**

# APPENDIX 1 : LIST OF DOCUMENTS TO BE GENERATED BEFORE AND KEPT DURING AND AFTER COMPLETION/TERMINATION OF THE TRIAL (ADAPTED FROM ICH-GCP)

#### **Before the Clinical Phase of the Trial Commences**

During this planning stage the following documents should be generated and should be on file before the trial formally starts:

Title of Document	Purpose	
Investigator's Brochure (or Product Information document for a marketed product- see SOP004 section 4.4)	To document that relevant and current scientific information about the investigational product has been provided to the investigator.	
Signed protocol and amendments, if any, and sample Case Report Form (CRF)	To document investigator and sponsor agreement to the protocol/amendment(s) and CRF.	
<ul> <li>Information given to trial subject:         <ul> <li>Informed Consent Form (including all applicable translations)</li> <li>Any other written information</li> </ul> </li> <li>Advertising for subject recruitment (if used)</li> </ul>	To document the informed consent.  To document that subjects will be given appropriate written information (content and wording) to support their ability to give fully informed consent.  To document that recruitment measures are appropriate and not coercive.	
Financial aspects of the trial	To document the financial agreement between the investigator/institution and the sponsor for the trial.	
Insurance statement (where required)	To document that compensation to subject(s) for trial-related injury will be available.	
Signed agreement between involved parties e.g.:  Investigator/institution and sponsor Investigator/institution and CRO Sponsor and CRO Investigator/institution and authority(ies) (where required)	To document agreements.	

Title of Document	Purpose
Dated, documented approval/favourable opinion of Institutional Review Board (IRB)/Independent Ethics Committee (IEC) of the following:  • Protocol and any amendments • CRF (if applicable) • Informed consent form(s) • Any other written information to be provided to the subject(s) • Advertisement for subject recruitment (if used) • Subject compensation (if any) • Any other documents given approval/favourable opinion	To document that the trial has been subject to IRB/IEC review and given approval/favourable opinion. To identify the version number and date of the document(s).
Institution Review Board/Independent Ethics Committee Composition	To document that the IRB/IEC is constituted in agreement with GCP.
Regulatory authority(ies) authorisation/ approval/notification of protocol (where required)	To document appropriate authorisation/approval/ notification by the regulatory authority(ies) has been obtained prior to initiation of the trial in compliance with the applicable regulatory requirement(s).
Curriculum Vitae and/or other relevant documents evidencing qualifications of investigator(s) and sub-investigator(s)	To document qualifications and eligibility to conduct trial and/or provide medical supervision of subjects.
Normal value(s)/range(s) for medical/laboratory/ technical procedure(s) and/or test(s) included in the protocol	To document normal values and/or ranges of the tests.
Medical/laboratory/technical procedures/tests:	To document competence of facility to perform required test(s) and support reliability of results.
Instructions for handling of investigational product(s) and trial-related materials (if not included in protocol or Investigator's Brochure)	To document instructions needed to ensure proper storage, packaging, dispensing and disposition of investigational products and trial-related materials.
Shipping records for investigational product9s) and trial-related materials	To document shipment dates, batch numbers and method of shipment of investigational product(s) and trial-related materials. Allows tracking of product batch, review of shipping conditions and accountability.

Title of Document	Purpose
Decoding procedures for blinded trials	To document how, in case of an emergency, identity of blinded investigational product can be revealed without breaking the blind for the remaining subjects' treatment.
Trial initiation monitoring report	To document that trial procedures were reviewed with the investigator and the investigator's trial staff.

# **During the Clinical Conduct of the Trial**

In addition to having on file the above documents, the following should be added to the files during the trial as evidence that all new relevant information is documented as it becomes available:

Title of Document	Purpose
Investigator's Brochure Updates	To document that investigator is informed in a timely manner of relevant information as its becomes available.
Any revision to:	
<ul> <li>Protocol/amendment(s) and CRF</li> <li>Informed consent form</li> <li>Any other written information provided to subjects</li> <li>Advertisement for subject recruitment (if used)</li> </ul>	To document revisions of these trial related documents that take effect during the trial.
Dated, documented approval/favourable opinion of Institutional Review Board (IRB)/Independent Ethics Committee (IEC) of the following:	To document that the amendment(s) and/or revision(s) have been subject to IRB/IEC review and were given approval/favourable opinion. To identify the version number and date of the document(s).
<ul><li>Protocol amendment(s)</li><li>Revision(s) of:</li></ul>	
<ul> <li>Informed consent form</li> </ul>	
<ul> <li>Any other written information to be provided to the subject</li> </ul>	
<ul> <li>Advertisement for subject recruitment (if used)</li> </ul>	
<ul> <li>Any other documents given approval/favourable opinion</li> </ul>	
<ul> <li>Continuing review of trial (where required</li> </ul>	
Regulatory authority(ies) authorisations/ approvals/notifications where required for:	To document compliance with applicable regulatory requirements.
<ul> <li>Protocol amendment(s) and other documents</li> </ul>	

VMIA SOP No. 002

Title of Document	Purpose
Curriculum vitae for new investigator(s) and/or sub-investigator(s)	
Updates to normal value(s)/range(s) for medical/laboratory/technical procedure(s)/ test(s) included in the protocol	To document normal values and ranges that are revised during the trial.
Updates of medical/laboratory/technical procedures/tests:	To document that tests remain adequate throughout the trial period.
<ul> <li>Certification; or</li> <li>Accreditation; or</li> <li>Established quality control and/or external quality assessment; or</li> <li>Other validation (where required)</li> </ul>	
Documentation of investigational product(s) and trial-related materials shipment	
Relevant communications other than site visits:      Letters     Meeting notes     Notes of telephone calls	To document any agreements or significant discussions regarding trial administration, protocol violations, trial conduct, adverse event (AE) reporting.
Signed informed consent forms	To document that consent is obtained in accordance with GCP and protocol and dated prior to participation of each subject in trial. Also to document direct access permission.
Source documents	To document the existence of the subject and substantiate integrity of trial data collected. To include original documents related to the trial, to medical treatment, and history of subject.
Signed, dated and completed case report forms (CRF)	To document that the investigator or authorised member of the investigator's staff confirms the observations recorded.
Documentation of CRF corrections	To document all changes/additions or corrections made to CRF after initial data were recorded.
Notification by originating investigator to sponsor of serious adverse events and related reports	Notification by originating investigator to sponsor of serious adverse events and related reports.
Notification by sponsor and/or investigator, where applicable to regulatory authority(ies) and IRB(s)/IEC(s) of unexpected serious adverse drug reactions and of other safety information	Notification by sponsor and/or investigator, where applicable, to regulatory authorities and IRB(s)/IEC(s) of unexpected serious adverse drug reactions and other safety information.

Title of Document	Purpose
Notification by sponsor to investigator of safety information	Notification by sponsor to investigators of safety information.
Interim or annual reports to IRB/IEC and authority(ies)	Interim or annual reports provided to IRB/IEC and to authority(ies).
Subject screening log	To document identification of subjects who entered pre-trial screening.
Subject identification code list	To document that investigator/institution keeps a confidential list of names of all subjects allocated to trial numbers on enrolling in the trial. Allows investigator/institution to reveal identity of any subject.
Subject enrolment log	To document chronological enrolment of subjects by trial number.
Investigational products accountability at the site	To document that investigational product(s) have been used according to the protocol.
Signature sheet	To document signatures and initials of all persons authorised to make entries and/or corrections on CRFs.
Record of retained body fluids/tissue samples (if any)	To document location and identification of retained samples if assays need to be repeated.

## **APPENDIX 2: SOP CHANGE LOG**

Reason for Issue	
First issue	

## **APPENDIX 3: SITE MASTER FILE CONTENTS TEMPLATE**

File Section	Documentation	Done
Contact List	Contact list table for study related personnel	
Correspondence	General correspondence with sponsor, CRO, teleconference and meeting notes	
Agreements	Clinical trial agreement location, site indemnities, confidentiality agreement(s) location, letters of intent	
Finance	Financial disclosure forms for any person listed on the FDA Form 1572 (IND study only)	
Ethics committee 5.1. Ethics Committee Approvals/ Acknowledgements 5.2. Ethics Committee Composition 5.3. Ethics Committee Correspondence	All ethics correspondence and documentation including all versions of the informed consent form, ethics committee composition, statement of committee compliance to NH&MRC National Statement, approval letters, reports to ethics committee, correspondence as applicable to commercial sponsorship, submission package(s), sample informed consent form, approved advertising materials/wording, other information provided to study subjects and approved by ethics, tracked changes to protocol and summary tables, insurance certificate	
Investigator's Brochure and safety updates	All versions as provided to ethics, safety updates from sponsor	
Protocol	All versions as provided to and as approved by ethics, signed protocol signatory page should also be in this section	
Regulatory documents	Australian CTX or CTN form (fully executed), IND form 1572, other regulatory agency forms, all correspondence to the regulatory agencies	
Sample CRF	Approved version of sample CRF (a blank set that can be duplicated)	
Serious Adverse Events	Documentation tracking the incidence and reporting of SAEs, reports to ethics, reports to the applicable agency (interim and final)	
Monitoring	All general monitoring correspondence unless specifically belonging in another file section, pre-trial monitoring report, feasibility assessments, monitoring visit reports and follow-up letters, monitor-site correspondence, close-out visit reports	
Audit	Auditor correspondence, audit reports (if available) and auditor follow-up letters	
Laboratory	Clinical laboratory certification (NATA, CLIA), laboratory normal values for medical/laboratory/technical procedures and/or tests included in the protocol, all laboratory related correspondence	
Curriculum vita	Signed and dated copies of <i>curriculum vita</i> for all medical staff, principal investigator, sub-investigators updated to include current positions. CVs should be present for all those listed on the delegations log	

File Section	Documentation	Done
Signature log	Site personnel signature sheet with a list of signatures and initials of all persons authorised to make entries and/or corrections on the CRFs and certain delegated tasks	
CRF completion guidelines	Any correspondence, presentations and/or CRF completion guidelines provided by the Sponsor	
Shipping records	Shipment records, date of shipment, batch numbers, method, shipment receipt records, certificate of analysis for investigational product, storage conditions. Shipping details of other study related documentation or materials should also be recorded.	
Accountability records	Investigational product accountability correspondence and/or records	
Decoding and unblinding	Any correspondence relating to decoding and unblinding.  Documents how identity of blinded investigational product can be revealed in case of emergency.	
Subject screening logs	Screening logs including participant identification logs (site only for identification in case of emergency), participant registration/screening logs containing a chronological listing of screening/enrolment of subjects	
Subject identification code list	A confidential list of names of all subjects allocated to trial numbers on enrolment in the trial. Allows investigator/institution to reveal subject identity	
Subject enrolment logs	Chronological enrolment of subjects by subject number	
Visit log	Records for all site visits, monitoring visits, sponsor visits, auditor visits, agency audits	
Data query tracking	Data query tracking, monitors site queries and correspondence	
Clinical study report	Final clinical study report (signed copy) if provided	
Signed Informed Consent Forms	Informed Consent forms should be fully signed with all signatories dating their own signature. In addition, time of consent should be recorded in order to establish that consent was obtained prior to any trial procedures. Where informed consent is placed in the medical record, a file note stating this must be added to this section of the file	
Other-study specific	Other documents not included in the previous sections	

## STANDARD OPERATING PROCEDURE

Title: Communication with HREC, Trial Sponsor and Insurer			
Document ID: 003			
Version: <insert as="" local="" management="" per="" quality="" site="" system="" version="" your=""></insert>			
Author: <insert approver="" author="" local="" name="" of="" or=""></insert>			
Author Signature:	Date: <insert date=""></insert>		
Effective Date: <insert date="" department="" effective="" from="" in="" institution="" is="" procedure="" that="" this="" your=""></insert>			
Review Before: <insert date="" of="" procedure<="" td="" this="" when=""><td>should be reviewed&gt;</td></insert>	should be reviewed>		
Department/institution name: < insert Department/in	stitution name>		
Reviewed and Approved by: <insert name=""></insert>	<insert position="" title=""></insert>		
Signature:	Date: <insert date=""></insert>		
Departmental Head: < insert name>			
Signature:	Date: <insert date=""></insert>		

VMIA SOP No. 003

#### 1. AIM

To describe the procedures related to communication with the HREC, trial sponsor and insurer.

#### 2. SCOPE

Applicable to all Phases of clinical investigation of medicinal products, medical devices and diagnostics.

#### 3. APPLICABILITY

Principal Investigator/Investigator, Sub-Investigator(s) and delegate(s).

#### 4. PROCEDURE

## 4.1 Communication with HREC

## The investigator(s) should:

- Understand the Institutional HREC requirements and processes to better liaise with sponsors – e.g. on application process, documents, understanding legal requirements, understanding specific institutional site specifications on wording in consent forms etc.
- Be aware of how often the HREC meets, what documents are required in an initial application and when (time period prior to an ethics committee meeting), what is the approval documentation and how to issue safety alerts.
- Ensuring they are familiar with this process (e.g. does the HREC have subcommittees) since this may be required to be described to sponsors, auditors, inspectors.
- Ensure the institutional ethics committee is registered with AHEC and is constituted in accordance with the National Statement.
- Obtain written and dated approval/favourable opinion from the HREC for the trial protocol, written informed consent form, consent form updates, subject recruitment procedures (e.g. advertisements), and any other written information to be provided to subjects prior to the commencement of the trial. This is normally in the form of an ethics approval letter which should state the version number and dates of documentation submitted.
- As part of the institution's written application to the HREC, provide the HREC with a current copy of the Investigator's Brochure and if updated during the trial, the investigator/institution should supply a copy to the HREC.

VMIA SOP No. 003

- Be familiar with the procedure for submitting protocol amendments and changes to the informed consent form and understand the time periods associated to obtain approval following submission of amendments.
- Provide to the HREC all documents subject to review during the trial, including any serious or unexpected adverse events, proposed changes in the protocol and unforseen events that might affect continued ethical acceptability of the project.
- Submit written summaries of the trial status to the HREC annually, or more frequently, if requested by the HREC. They should understand the reporting requirements for their ethics committee including protocol deviations and safety reporting.
- In addition, the Investigator must report to the HREC any serious, adverse drug/device effect that is experienced during the Trial by any participant within 24 hours of him or her becoming aware of same.

## 4.2 Communication with the Trial Sponsor

## The investigator(s) should:

- Notify the sponsor within 24 hours of any serious or unexpected adverse events involving trial subjects.
- Provide written reports promptly to the sponsor, the HREC and, where applicable, the institution on any changes significantly affecting the conduct of the trial, and/or increasing the risk to subjects.
- notify the sponsor within 24 hours of any significant deviation from the protocol (this is individually defined by the sponsor).
- Notify the sponsor promptly of any adverse effect that may reasonably be regarded as caused by, or probably caused by, the investigational product.
- Be available during the study to meet with sponsor delegates to discuss study progress, issues and safety.

VMIA SOP No. 003

## 4.3 Communication with the Insurer

## **Obligation of the Institution:**

The institution must report the following to the VMIA (usually through the ethics committee:

- Reports of serious adverse events, [or which relate to a claim made against the
  Hospital/institution (or member of its staff) and/or the occurrence of circumstances
  which may subsequently give rise to a claim against a Hospital/Institution], must
  be reported to VMIA in accordance with the provisions of the VMIA Public Liability
  and Medical Indemnity Policies. VMIA recommends the use of the pro forma
  Adverse Events Report Form.
- In addition to the requirements of the NHMRC National Statement, all serious adverse events that occur within the hospital or institution, that are possibly or likely to be related to any trial conducted by that hospital or institution.
- It is usually sufficient to fax or email a copy of the SAE report with a cover letter/email. Notification to the VMIA should occur as promptly as possible upon becoming aware of the SAE.

Note: Failure to give proper, prompt notification of any circumstance likely to give rise to a claim or the making of a claim may compromise insurance coverage for both the Hospital/Institution and/or a member of its staff.

## 5. GLOSSARY

#### **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 subjects are protected.

## **Human Research Ethics Committee (HREC)**

A body which reviews research proposals involving human participants to ensure that they are ethically acceptable and in accordance with relevant standards and guidelines.

VMIA SOP No. 003

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, 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.

## **Serious Adverse Device Event (SADE)**

A device-related serious adverse event. (See Serious Adverse Event (SAE) – device).

## Serious Adverse Event (SAE) - drug

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 patient 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 in-patient hospitalisation or prolongation of existing hospitalisation;
- d. results in persistent or significant disability/incapacity; or
- e. is a congenital anomaly/birth defect; and fits the SAE criteria as specified in the relevant clinical trial protocol.

Medical or scientific judgment 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 subject or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These should also usually be considered serious. Examples of such events are intensive treatment in an emergency room or at home for

VMIA SOP No. 003

allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalisation; or development of drug dependency or drug abuse.

## Serious Adverse Event (SAE) - device

Serious Adverse Event for *medical devices*: any adverse medical occurrence that:

- a. lead to a death;
- b. lead to a serious deterioration in health of a patient user or other. This would include:
  - a life threatening illness or injury
  - a permanent impairment of body function or permanent damage to a body structure
  - a condition requiring hospitalisation or increased length of existing hospitalisation
  - a condition requiring unnecessary medical or surgical intervention e) foetal distress, foetal death or a congenital abnormality/birth defect
- c. might have led to a death or a serious deterioration in health had suitable action or intervention not taken place.

## This includes:

- a malfunction of a device such that it has to be modified or temporarily/permanently taken out of service
- a factor (a deterioration in characteristics or performance) found on examination of the device.

## **Sub Investigator**

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

VMIA SOP No. 003

## 6. REFERENCES

- 1. Note for guidance on Good Clinical Practice (CPMP/ICH/135/96) annotated with TGA comments DSEB, July 2000.
- 2. Victorian Managed Insurance Authority Guidelines for Clinical Trials for Victorian Public Hospitals (CTN guidelines), 2006.

## 7. APPENDICES

Appendix 1: SOP Change Log

## **DOCUMENT END**

VMIA SOP No. 003

COMMUNICATION WITH HREC, TRIAL SPONSOR AND INSURER

Version: 1.0 Dated 17 September 2007

## **APPENDIX 1: SOP CHANGE LOG**

Version No.	Reason for Issue
1	First issue

VMIA SOP No. 003

## STANDARD OPERATING PROCEDURE

# Title : Protocol and Investigational Brochure Content, Design, Amendments & Compliance

Document ID: 004			
Version: <insert as="" local="" management="" per="" quality="" site="" system="" version="" your=""></insert>			
Author: <insert approver="" author="" local="" name="" of="" or=""></insert>			
Author Signature:	Date: <insert date=""></insert>		
Effective Date: <insert date="" department="" effective="" from="" in="" institution="" is="" procedure="" that="" this="" your=""></insert>			
Review Before: <insert be="" date="" of="" procedure="" reviewed="" should="" this="" when=""></insert>			
Department/institution name: < insert Department/institution name>			
Reviewed and Approved by: <insert name=""></insert>	<insert position="" title=""></insert>		
Signature:	Date: <insert date=""></insert>		
Departmental Head: < insert name>			
Signature:	Date: <insert date=""></insert>		

VMIA SOP No. 004

PROTOCOL AND INVESTIGATIONAL BROCHURE CONTENT, DESIGN, AMENDMENTS & COMPLIANCE

Version: 1.0 Dated 17 September 2007

#### 1. AIM

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

#### 2. SCOPE

Applicable to all phases of clinical investigation of medicinal products, medical devices, diagnostics and therapeutic interventions.

## 3. APPLICABILITY

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

#### 4. PROCEDURE

## 4.1 Protocol content and design

Specific content of a protocol 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.

Where the investigator is responsible for the protocol design and /or 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) 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 trial-site related medical (or dental) decisions (if other than investigator).
- Name(s) and address(es) of the clinical laboratory(ies) and other medical and/or technical department(s) and/or institutions involved in the trial.

VMIA SOP No. 004

PROTOCOL AND INVESTIGATIONAL BROCHURE CONTENT, DESIGN, AMENDMENTS & COMPLIANCE

## **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 trial.
- Summary of the known and potential risks and benefits, if any, to human subjects.
- Description of and justification for the route of administration, dosage, dosage regimen, and treatment period(s).
- 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 trial, and that provide background for the trial.

## **Trial Objectives and Purpose**

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

## Trial Design

- The scientific integrity of the trial and the credibility of the data from the trial depend substantially on the trial design. A description of the trial design should include:
  - a. A specific statement of the primary endpoints and the secondary endpoints, if any, to be measured during the trial.
  - b. A description of the type/design of trial to be conducted (e.g. double-blind, placebo controlled, parallel design) and a schematic diagram of trial design, procedures and stages.
- A description of the measures taken to minimize/avoid bias, including:
  - a. Randomization.
  - b. Blinding.
- A description of the trial treatment(s) and the dosage and dosage regimen of the investigational product(s). Also include a description of the dosage form, packaging, and labelling of the investigational product(s).

- The expected duration of subject participation, and a description of the sequence and duration of all trial periods, including follow-up, if any.
- A description of the "stopping rules" or "discontinuation criteria" for individual subjects, parts of trial and entire trial.
- Accountability procedures for the investigational product(s), including the placebo(s) and comparator(s), if any.
- Maintenance of trial treatment randomization codes and procedures for breaking codes.
- The identification of any data to be recorded directly on the CRFs (i.e. no prior written or electronic record of data), and to be considered to be source data.

## **Selection and Withdrawal of Subjects**

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

#### **Treatment of Subjects**

- 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 subjects 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 subject compliance.

## Assessment of Efficacy

VMIA SOP No. 004

PROTOCOL AND INVESTIGATIONAL BROCHURE CONTENT, DESIGN, AMENDMENTS & COMPLIANCE

- 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 intercurrent illnesses.
- The type and duration of the follow-up of subjects after adverse events.

#### **Statistics**

- A description of the statistical methods to be employed, including timing of any planned interim analysis(ses).
- The number of subjects planned to be enrolled. In multicentre trials, the numbers of enrolled subjects projected for each trial 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 subjects to be included in the analyses (e.g. all randomized subjects, all dosed subjects, all eligible subjects, evaluable subjects).

## **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 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.

## **Supplements**

## 4.2 Amendments to the protocol

## The investigator(s) should:

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

## 4.3 Protocol compliance

## The investigator(s) should:

 Conduct the 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.

VMIA SOP No. 004

Version: 1.0 Dated 17 September 2007

- Along with the sponsor, sign the protocol, or an alternative contract, to confirm agreement.
- Not implement any deviation from, or changes to the protocol without agreement by the sponsor and prior review and documented approval/favourable opinion from the HREC of an amendment, except where necessary to eliminate an immediate hazard(s) to trial subjects, 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 subjects without prior HREC approval/favourable opinion.

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

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

## 4.4 Investigational brochure content and design

Specific content of an Investigational Brochure will vary depending on whether the 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 subjects.

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

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

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

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

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

"If the investigational product is marketed and its pharmacology is widely understood by medical practitioners, an extensive IB may not be necessary. Where permitted by regulatory authorities, a basic product information brochure, package leaflet, or labelling may be an appropriate alternative, provided that it includes current, comprehensive, and detailed information on all aspects of the investigational product that might be of importance to the investigator. If a marketed product is being studied for a new use (i.e, a new indication), an IB specific to that new use should be prepared."

## 4.5 The Investigator Brochure should provide the following information:

## Title Page

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

## **Confidentiality Statement**

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

#### **Contents of the Investigator's Brochure**

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

## **Table of Contents**

#### Summary

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

#### Introduction

- A brief introductory statement should be provided that contains:
- The chemical name (and generic and trade name(s) when approved) of the investigational product(s).
- All active ingredients, the investigational product (s) pharmacological class and its expected position within this class (e.g. advantages).
- The rationale for performing research with the investigational product(s), and the anticipated prophylactic, therapeutic, or diagnostic indication(s).
- The introductory statement should provide the general approach to be followed in evaluating the investigational product or device.

## Physical, Chemical, and Pharmaceutical Properties and Formulation

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

#### **Non-Clinical Studies**

#### Introduction

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

VMIA SOP No. 004

PROTOCOL AND INVESTIGATIONAL BROCHURE CONTENT, DESIGN, AMENDMENTS & COMPLIANCE

- · 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
  - I. 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.

VMIA SOP No. 004

PROTOCOL AND INVESTIGATIONAL BROCHURE CONTENT, DESIGN, AMENDMENTS & COMPLIANCE

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/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**

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

## **Good Clinical Practice (GCP)**

A standard for the design, conduct, performance, monitoring, auditing, recording, analyses, and reporting of clinical trials that provides assurance that the data and reported results are credible and accurate, and that the rights, integrity, and confidentiality of trial subjects are protected.

#### **Human Research Ethics Committee (HREC)**

A body which reviews research proposals involving human participants to ensure that they are ethically acceptable and in accordance with relevant standards and guidelines.

The National Statement requires that all research proposals involving human participants be reviewed and approved by an HREC and sets out the requirements for the composition of an HREC.

## **International 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, 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 & 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 subjects. For marketed products it may be acceptable to use the Product Information. (see 4.4 above).

## **Protocol**

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

## **Sub Investigator**

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

## 6. REFERENCES

- 1. Note for guidance on Good Clinical Practice (CPMP/ICH/135/96) annotated with TGA comments DSEB, July 2000.
- NHMRC National Statement on Ethical Conduct in Human Research, 2007.

## 7. APPENDICES

Appendix 1: SOP Change Log

Appendix 2: ICH standard protocol template

Appendix 3: ICH standard investigational brochure template

VMIA SOP No. 004

PROTOCOL AND INVESTIGATIONAL BROCHURE CONTENT, DESIGN, AMENDMENTS & COMPLIANCE

## **DOCUMENT END**

Version: 1.0 Dated 17 September 2007

## **APPENDIX 1: SOP CHANGE LOG**

Version No.	Reason for Issue
1	First issue

## **CONFIDENTIAL**

## PROTOCOL TITLE

**Protocol No: XXXX** 

Version: XXXX Date: XXXXX

## **SPONSOR**

Company Name

**ADDRESS** 

XXXXXXX

XXXXXXX

Phone: XXXXXXX

## PRINCIPAL CLINICAL INVESTIGATOR

PRINCIPAL INVESTIGATOR NAME

**ADDRESS** 

XXXXXXX

XXXXXXX

Phone: XXXXXXX

## AMENDMENTS:

Protocol No.: XXXXXX

1.	2.	3.	4.

## AUTHORS NAME AND ADDRESS OF AUTHOR

STUDY CENTRE NAME, ADDRESS AND TELEPHONE NUMBER OF STUDY CENTRE

BIOSTATISTICIAN NAME AND ADDRESS OF STATISTICIAN (IF APPLICABLE)

STUDY MONITOR NAME AND ADDRESS OF STUDY MONITOR

SPONSOR'S MEDICAL REPRESENTATIVE NAME AND ADDRESS OF SPONSOR'S MEDICAL EXPERT (if different from investigator)

## 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<sup>[1]</sup> (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 there from 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	Signature
INVESTIGATOR – NAME	

AND TITLE Date:

**Sponsor Signatory:** 

COMPANY NAME Signature: SIGNATORY – NAME AND

TITLE Date:

Protocol No.: XXXXXX Company Name - CONFIDENTIAL VERSION DATE

## **Table of Contents**

Protocol No.: XXXXXX

ΡI	ROTOC	COL TITLE	1
1	Synopsis		
2			
3	J		
4	Study Design		
5	Study Population		
	5.1	Number of subjects	0
	5.2	Inclusion Criteria1	0
	5.3	Exclusion Criteria	1
	5.4	Other Eligibility Criteria Considerations	1
6	Stud	y Assessments and Procedures1	1
	6.1	Screening Evaluation	1
		Study Procedures	1
	6.2.1	Baseline (Day 0)1	1
	6.2.2	2 Day 11	1
	6.2.3	Follow-Up Visit1	1
	6.3	Efficacy Assessments	2
	6.4	Study Restrictions	2
	6.4.1	Dietary1	2
	6.4.2	2 Smoking1	2
	6.4.3	3 Confinement1	2
	6.4.4	Position / Ambulation	2
	6.4.5	Concomitant Medication1	2
	6.4.6	Other Restrictions	2
	6.5	Safety Assessments	2
	6.5.1	Physical Examination1	2
	6.5.2	2 Vital Signs1	2
	6.5.3	3 12-Lead ECG	2
	6.5.4	Laboratory Safety Testing1	2
	6.5.5	5 Adverse Events	3
	6.5.6	Other Safety Assessments	3
	6.6	Pharmacokinetic Sampling	3
	6.7	Pharmacodynamic Sampling	3
7	Inve	stigational product(s)1	4
	7.1	Description of Investigational Product(s)	4
	7.2	Dose Justification	4
	7.3	Comparator Justification	4
	7.4	Administration1	4
	7.5	Randomisation	4

Protocol No.: XXXXXX

	7.6	Unblinding	.14
	7.7	Product Labelling	.14
	7.8	Handling and Storage of Study Drugs	.14
8	Adv	erse Events (AE) and Serious Adverse Events (SAE)	.14
	8.1	Definition of an Adverse Event (AE)	
	8.2	Definition of a Serious Adverse Event (SAE)	.15
	8.3	Clinical Laboratory Abnormalities and Other Abnormal Assessments	as
	AEs ar	d SAEs	
	8.4	Time Period, Frequency, and Method of Detecting AEs and SAEs	.17
	8.5	Recording of AEs and SAEs	.17
	8.6	Prompt Reporting of SAEs to Company Name	17
	8.7	Expeditable Events	18
	8.8	Evaluating AEs and SAEs	18
	8.8.1	Assessment of Intensity	18
	8.8.2	2 Assessment of Causality	.19
	8.8.3	3 Assessment of Expectedness	.20
	8.9	Follow-up of AEs and SAEs	.20
	8.10	Post-study AEs and SAEs	.20
9	Subj	ect Completion and Discontinuation	21
	9.1	Subject Completion	.21
	9.2	Stopping Rules / Discontinuation Criteria	.21
	9.3	Subject Withdrawal	.21
	9.4	Early Termination of the Study	21
10	) C	ase Report Form (CRF)	.21
1		ata Analysis and Statistical Considerations	
	11.1	Hypotheses	.22
	11.2	Endpoints	.22
	11.3	Sample Size	.22
	11.4	Statistical Analysis	.22
	11.5	Additional Analyses	.22
12	2 D	ata Management	.23
13		onitoring and Quality Assurance	
	13.1	Curriculum Vitae and Other Documentation	.23
14	4 In	vestigator Responsibility	.23
1.		udy Report	
10		dministrative Procedures	
	16.1	Ethical Considerations	
	16.2	Ethical Review Committee	
	16.3	Regulatory Authorities	
	16.4	Informed Consent	25

Protocol No.: XXXXXX

16.5 Subject Reimbursement .......25 16.6 16.7 16.8 16.9 16.10 16.11 Archives: Retention of Study Records......27 16.12 16.13 Archives: Retention of Other Study Specific Samples .......27 17 

## ABBREVIATIONS AND DEFINITIONS OF TERMS

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 m<sup>2</sup>)

C<sub>max</sub> 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

Protocol No.: XXXXXX

WBC White Blood Cells

Protocol No.: XXXXXX

1	Synopsis
Stu	dy Title:
Pro	tocol Number:
Dev	velopment Phase:
Ind	ication:
(Incom	dy Drugs: cluding test, nparator, dosage m, dosing regimen l route)
No.	Subjects:
No.	Centres:
Stu	dy Duration:
Obj Stu	jectives of the dy:
(Pr	dy Endpoints: imary and ondary)
Stu	dy Design:
(Inc	gibility Criteria clusion and clusion)
	dy Procedures:

Protocol No.: XXXXXX

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 subjects; 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 subject descriptor as appropriate.

#### 5.1 Number of subjects

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

#### 5.2 Inclusion Criteria

Protocol No.: XXXXXX

All subject 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 subject 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 subject 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

Protocol No.: XXXXXX

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

Protocol No.: XXXXXX

- 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 subject 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 subject 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, subjects 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

Protocol No.: XXXXXX

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

#### **Investigational product(s)** 7

#### 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**

#### 7.6 **Unblinding**

#### 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.

#### Adverse Events (AE) and Serious Adverse Events (SAE) 8

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 patient or clinical investigation subject, 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 subjects' 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

Protocol No.: XXXXXX

b) is life threatening

Note: The term 'life-threatening' in the definition of 'serious' refers to an event in which the subject 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 subject 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 out-patient 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.

Protocol No.: XXXXXX

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 subject 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.

# 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 subject'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.

Page 16 of 29
Company Name - <u>CONFIDENTIAL</u> VERSION DATE

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 subject 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) subjects will be asked:

"How are you feeling?"

Protocol No.: XXXXXX

At subsequent scheduled intervals subjects 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 subject'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 subject 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 subject'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 subject, 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

Page 17 of 29
Company Name - CONFIDENTIAL VERSION DATE

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 local IEC requirements, the investigator must also notify their Ethics Committee of any SAEs according the guidelines of the Ethics Committee.

The investigator, and others responsible for subject 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 subject 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 subject due to an inability to contact Company Name.

#### 8.7 Expeditable Events

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

Protocol No.: XXXXXX

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 subject, 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 predefined 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 subject'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 and cannot be reasonably explained by the known

characteristics of the study subject'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.

Page 19 of 29
Protocol No.: XXXXXX Company Name - CONFIDENTIAL VERSION DATE

#### 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 subject and provide further information to Company Name on the subject'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 subject 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

Protocol No.: XXXXXX

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 subject 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 Subject Completion and Discontinuation

#### 9.1 Subject Completion

The definition of a completed subject should be provided.

#### 9.2 Stopping Rules / Discontinuation Criteria

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

#### 9.3 Subject Withdrawal

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

#### 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 subjects.

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

After such a decision, the Investigator must contact all participating subjects within two weeks, and written notification must be sent to the Ethics Committee.

#### 10 Case Report Form (CRF)

Protocol No.: XXXXXX

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

Page 21 of 29
Company Name - CONFIDENTIAL

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 in to primary and secondary.

#### 11.3 Sample Size

The following should be considered and included in this section: Number of subjects planned to be enrolled - in multicentre trials, the numbers of enrolled subjects 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 subjects to be included in the analyses (e.g. all randomised subjects, all dosed subjects, all eligible subjects, evaluable subjects 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

Protocol No.: XXXXXX

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 subject 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.

#### 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<sup>[1]</sup>.

Page 23 of 29
Protocol No.: XXXXXX Company Name - CONFIDENTIAL VERSION DATE

#### 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 subjects. 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<sup>[1]</sup>.

#### 16.2 Ethical Review Committee

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

It is the responsibility of the Investigator to report study progress to the Ethics Committee 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 Ethics Committee as soon as possible, and in accordance with the guidelines of the Ethics Committee.

#### 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.

Page 24 of 29
Protocol No.: XXXXXX Company Name - CONFIDENTIAL VERSION DATE

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 Subject 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 subjects 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 subject'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 subject.

#### 16.5 Subject Reimbursement

#### If applicable.

Protocol No.: XXXXXX

Each subject will be reimbursed for out of pocket expenses, inconvenience and time involved. Such reimbursement is standard practice in studies such as this. If the study is terminated by Company Name or the Investigator(s) prior to completion, or a subject withdraws or is withdrawn from the study before completion, a pro-rata payment will be made at the discretion of the Investigator(s). Reserve subjects will also be reimbursed for inconvenience and time involved.

#### **16.6 Emergency Contact with Investigators**

All subjects will be provided with a Subject 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 volunteer, it is the Investigator's responsibility to notify the primary care physician of the subject's participation in the study, provided that such a physician can be identified for the subject. 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.

Page 25 of 29
Company Name - CONFIDENTIAL

VERSION DATE

#### 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 subjects 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

Protocol No.: XXXXXX

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 subject 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 appropriate 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 Ethics Committee.

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 subjects 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 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 subjects, each subject's consent to continue participation should be obtained.

Protocol No.: XXXXXX

#### 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 subject 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 shall be recorded in the CRF.

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<sup>[1]</sup>.

#### 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

Protocol No.: XXXXXX

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 1 – Study Schedule of Event

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

Page 29 of 29 Company Name - CONFIDENTIAL

Protocol No.: XXXXXX

VERSION DATE

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# **CLINICAL INVESTIGATOR'S BROCHURE**

Investigational product:	
Research name/number:	
INN name:	
Indication:	
Sponsor	
Telephone:	
Fax:	
Email:	
Edition:	
Release Date:	
This document supersedes Edition number: X.0 dated:	
CONFIDENTIALITY STATEMENT	
[insert]	

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#### **SPONSOR STATEMENT**

This Clinical Investigator's Brochure (Confollowing persons:	CIB) was subject to critical review	v and has been approved by the
Signature		
Name: Add position (medical) Company		
Signature	 Date	
Name Add position (Scientific) Company		

# **TABLE OF CONTENTS**

1.	SUMN	IARY	8
	1.1. E	BACKGROUND	8
	1.2.	OVERVIEW OF INVESTIGATIONAL PRODUCT	8
	1.3.	CHEMISTRY, MANUFACTURING AND CONTROLS	8
	1.4. N	Nonclinical Studies	8
	1.4.1.	Pharmacology	8
	1.4.2.	Pharmacokinetics	8
	1.4.3.	Toxicology	8
		CLINICAL EXPERIENCE	
	1.6.	DEVELOPMENT PLAN	8
2.	INTRO	DDUCTION	9
	2.1.	OVERVIEW OF TARGETED DISEASE AND INDICATION	9
	2.2. I	NVESTIGATIONAL PRODUCT	9
	2.3. F	RATIONALE FOR CLINICAL DEVELOPMENT	9
	2.4.	OSE JUSTIFICATION	9
3.	PHYS	ICAL, CHEMICAL AND PHARMACEUTICAL PROPERTIES AND FORMULATION	10
	3.1.	DRUG SUBSTANCE	10
	3.1.1.	Manufacture	
	3.1.2.	Analysis and characterisation of IP	10
	3.1.3.	Stability	11
	3.2. I	NVESTIGATIONAL PRODUCT	11
	3.2.1.	Formulation	11
	3.2.2.	Manufacturer	11
	3.2.3.	Final dosage form and presentation	11
	<i>3.2.4.</i>	Posology	11
	3.2.5.	Container and packaging	11
	3.2.6.	Storage and handling	11
	3.2.7.	Stability	
	3.3.	DEVELOPMENT PHARMACEUTICS	12
4.	NON-	CLINICAL STUDIES	13
	4.1. N	NONCLINICAL PHARMACOLOGY	13
	4.1.1.	Summary	13
	4.1.2.	In vitro Pharmacology	13
	4.1.3.	In vivo Pharmacology	13
	4.1.4.	Mechanism of action	
	4.2. F	PHARMACOKINETICS AND PRODUCT METABOLISM IN ANIMALS	13
	4.2.1.	Summary	13
	4.2.2.	Method of Analysis	
	4.2.3.	Single-dose Absorption, Distribution, Metabolism and Excretion	
	4.2.4.	Multiple-dose Absorption, Distribution, Metabolism and Elimination	14

4	<i>4.2.5.</i>	Drug interactions	14
4.3.	. Т	OXICOLOGY AND SAFETY STUDIES	16
4	4.3.1.	Summary	16
4	4.3.2.	Acute toxicology	16
4	4.3.3.	Repeat dose toxicology	16
4	<i>1.3.4.</i>	Toxicokinetics	16
4	4.3.5.	Chronic toxicology	16
4	4.3.6.	Reproductive toxicology	16
4	4.3.7.	Safety pharmacology	16
4	4.3.8.	Genotoxicity (Mutagenicity)	19
4	4.3.9.	Carcinogenicity	19
4	4.3.10	Special studies	19
5. E	EFFEC	TS IN HUMANS	20
5.1.	. In	ITRODUCTION	20
5.2.		LINICAL DEVELOPMENT PROGRAM	
5.3.		HARMACOKINETICS, PHARMACODYNAMICS AND PRODUCT METABOLISM IN HUMANS	
5.4.		LINICAL EXPERIENCE	
5	5.4.1.	Dose response	20
5	5.4.2.	Safety and Efficacy	20
5	5.4.3.	Laboratory data and other safety parameters	21
5	5.4.4.	Individual study summaries	21
5	5.4.5.	Benefit – Risk Assessment	21
5.5.	. R	EGISTRATION AND MARKETING EXPERIENCE	21
6. 5	SUMM	ARY OF DATA AND GUIDANCE FOR THE INVESTIGATOR	22
6.1.	C	OMPOSITION	22
6.2.		RESENTATION	
6.3.		OSOLOGY AND ROUTE OF ADMINISTRATION	
6.4.		TORAGE AND STABILITY	
6.5.		HARMACOKINETICS OF INVESTIGATIONAL PRODUCT	22
6.6.	. В	IOANALYTICAL EVALUATION	22
6.7.	. N	ITIGATION OF OVERDOSE RISK	22
6.8.	. Е	XPEDITED SAFETY REPORTS	22
6.9.	. V	/ARNINGS, PRECAUTIONS	22
6.10	0. C	ONTRAINDICATIONS	22
6.1	1. A	DVERSE EVENTS	22
6.12	2. S	UBJECT POPULATIONS	22
$\epsilon$	5.12.1.	Pregnancy and Breast-Feeding	22
6	5.12.2	Paediatric Use	22
$\epsilon$	6.12.3	Geriatric Use	22
7. F	REFE	RENCES	24

# **LIST OF TABLES**

Table 2-1: Safety ratios for single oral doses	9
Table 3-1: Composition and characteristics of active ingredient	10
Table 3-2: General investigational drug product Information	11
Table 4-1: Mean plasma pharmacokinetic parameters for IP after single-dose administration	13
Table 4-2: Summary table of Pharmacology studies	15
Table 4-3: Summary table of Toxicology studies	18
Table 5-1: Pharmacokinetic parameters of IP following single-dose administration in study no	

# **LIST OF FIGURES**

# **LIST OF ABBREVIATIONS**

#### 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. <u>Pharmacokinetics</u>

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

- 2.1. Overview of targeted disease and indication
- 2.2. Investigational product
- 2.3. Rationale for clinical development
- 2.4. Dose justification

Table 2-1: Safety ratios for single oral doses

Human Single Dose	Rat NOAEL XX mg/kg/day	Dog NOAEL XXX mg/kg/day

# 3. PHYSICAL, CHEMICAL AND PHARMACEUTICAL PROPERTIES AND FORMULATION

## 3.1. Drug substance

The active pharmaceutical ingredient is

API is structurally similar to (add info)

Table 3-1: Composition and characteristics of active ingredient

NAME	
INTERNATIONAL NOMENCLATURE	
SPONSOR NAME	
CAS NUMBER	
STRUCTURE	
MOLECULAR FORMULA	
MOLECULAR WEIGHT	
DESCRIPTION	IP IS A SYNTHETIC XXXX. THE ACTIVE IS PRODUCED IN A SINGLE STEP FROM XXX WITH A PURITY TYPICALLY GREATER THAN 99%.  IP IS A WHITE TO OFF-WHITE CRYSTALLINE XXXX SALT WITH A PKA OF XX. THE MELTING POINT IS AROUND XX°C. THEACTIVE HAS A WATER SOLUBILITY OF XX MG/ML (AT PH XX).
ODOUR	
SOLUBILITY	
PROPERTIES	

#### 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

INGREDIENT	SPECIFICAT ION	PURPOSE	CONC (MG/ML)
ACTIVE	BP/USP??	ACTIVE	
EXCIPIENT		EXCIPIENT	
EXCIPIENT		EXCIPIENT	
EXCIPIENT		EXCIPIENT	
SOLUTE		SOLVENT	

#### 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°-30°C (59°-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

#### 4.1. Nonclinical Pharmacology

#### 4.1.1. **Summary**

#### 4.1.2. *In vitro* Pharmacology

4.1.2.1. Individual study summaries

#### 4.1.3. <u>In vivo Pharmacology</u>

#### 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. <u>Method of Analysis</u>

#### 4.2.3. Single-dose Absorption, Distribution, Metabolism and Excretion

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

Species	Ref	Dose (mg/kg)	Route	AUC <sub>inf</sub> (μg.h/mL)	C <sub>max</sub> (μg/mL)	CL (mL/kg/min)	V <sub>ss</sub> (L/kg)	T <sub>1/2</sub> (h)	F%
Mouse									
Rat									
Rabbit									
Dog									
Monkey									

- 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. <u>Multiple-dose Absorption, Distribution, Metabolism and Elimination</u>

4.2.4.1. Individual study summaries

## 4.2.5. **Drug interactions**

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Table 4-2: Summary table of Pharmacology studies

Results					
Duration					
Route of admin.					
Formulation Dose/Regimen Route of Duration Results admin.					
Formulation					
No/sex/ group					
Species/ No/sex/					
GLP					
Study number /Title					

Page 15 of 24 ; Version; Date:

## 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

Date: ; Version; Page 16 of 24

Investigator's Brochure Investigational Product

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Date: ; Version; Page 17 of 24

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Investigator's Brochure Investigational Product

Table 4-3: Summary table of Toxicology studies

Results					
Duration					
Route of admin.					
Formulation Dose/Regimen Route of Duration Results admin.					
Formulation					
No/sex/ group					
Species/ No/sex/					
GLP					
Study number /Title					

Page 18 of 24 ; Version;

Date:

Insert company logo

## 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

Date: ; Version; Page 19 of 24

## 5. EFFECTS IN HUMANS

## 5.1. Introduction

## 5.2. 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 patients.

## 5.3. Pharmacokinetics, Pharmacodynamics and Product Metabolism in Humans

Single doses of XX mg IP in healthy subjects resulted in linear and near dose-proportional increases in plasma concentrations of IP with increasing dose (mean  $C_{max}$  and AUC values increased XX-fold, respectively, overall). The mean  $C_{max}$  of IP ranged from XX–XX µg/mL, and the mean AUC<sub>0-inf</sub> ranged from XX-XX µg·h/mL. The mean  $T_{max}$  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.

Parameter	IP							
	200 mg (n=6)	500 mg (n=6)	1000 mg (n=6)					
C <sub>max</sub> (µg.h/mL)								
T <sub>max</sub> (h)								
T <sub>1/2</sub> (h)								
AUC <sub>0−24</sub> (μg⋅h/mL)								
AUC <sub>0-inf</sub> (μg·h/mL)								
CL (L/h)								

## 5.4. Clinical experience

## 5.4.1. <u>Dose response</u>

## 5.4.2. Safety and Efficacy

Date: ; Version; Page 20 of 24

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## 5.4.3. <u>Laboratory data and other safety parameters</u>

## 5.4.4. <u>Individual study summaries</u>

5.4.4.1. Study no.

5.4.4.2. Study no. (ongoing)

## 5.4.5. Benefit – Risk Assessment

## 5.5. Registration and Marketing experience

Ta date, IP has not been registered for use or marketed in any jurisdiction.

Date: ; Version; Page 21 of 24

## 6. SUMMARY OF DATA AND GUIDANCE FOR THE INVESTIGATOR

## 6.1. Composition

## 6.2. Presentation

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

- 6.3. Posology and route of administration
- 6.4. Storage and stability
- 6.5. Pharmacokinetics of investigational product
- 6.6. Bioanalytical evaluation
- 6.7. Mitigation of overdose risk
- 6.8. Expedited Safety Reports

## 6.9. 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.

## 6.10. Contraindications

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

## 6.11. Adverse events

## 6.12. Subject populations

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

## 6.12.1. 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.

## 6.12.2. Paediatric Use

No studies on the use of IP in paediatric subjects have been conducted.

## 6.12.3. Geriatric Use

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

Date: ; Version; Page 22 of 24

Investigator's Brochure Investigational Product

**CONFIDENTIAL** 

Insert company logo

Date: ; Version; Page 23 of 24

Insert company logo

## 7. REFERENCES

Date: ; Version; Page 24 of 24

## STANDARD OPERATING PROCEDURE

Title: Receipt and Handling of Inve	stigational Product
Document ID: 005	
Version: <insert as="" i<="" local="" per="" quality="" site="" td="" version="" your=""><td>management system&gt;</td></insert>	management system>
Author: <insert approver="" author="" local="" name="" of="" or=""></insert>	
Author Signature:	Date: <insert date=""></insert>
Effective Date: <insert date="" department="" effective="" is="" procedure="" that="" this=""></insert>	ctive from in your institution/
Review Before: <insert date="" of="" procedure="" sh<="" td="" this="" when=""><td>nould be reviewed&gt;</td></insert>	nould be reviewed>
Department/institution name: < insert Department/ins	stitution name>
Reviewed and Approved by: <insert name=""></insert>	<insert position="" title=""></insert>
Signature:	Date: <insert date=""></insert>
Departmental Head: < insert name>	
Signature:	Date: <insert date=""></insert>

VMIA SOP No. 005

RECEIPT AND HANDLING OF INVESTIGATIONAL PRODUCT

Version: 1.0 Dated 17 September 2007

## 1. AIM

To describe the procedures related to receipt and handling of investigational product.

## 2. SCOPE

Applicable to all phases of clinical investigation of medicinal products, medical devices and diagnostics.

## 3. APPLICABILITY

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

## 4. PROCEDURE

## 4.1 Receipt and handling of investigational product

Responsibility for investigational product(s) accountability at the trial site(s) rests with the investigator/institution.

## The investigator(s) should:

(Where allowed/required), assign some or all of the investigator's/institutions
duties for investigational product(s) accountability at the trial site(s) to an
appropriate pharmacist or another appropriate individual who is under the
supervision of the investigator/institution.

The investigator/institution and/or a pharmacist or other appropriate individual, who is designated by the investigator/institution, should:

- Maintain records of the product's delivery and receipt to the trial site, the
  inventory at the site, the use by each subject, and the return to the sponsor or
  alternative disposition of unused product(s). These records should include
  dates, quantities, batch/serial numbers, expiration dates (if applicable), and
  the unique code numbers assigned to the investigational product(s) and trial
  subjects.
- Ensure that the investigational product(s) are stored as specified by the sponsor in accordance with applicable regulatory requirement(s). Consideration should be given to how the investigational product shall be securely stored, including restricting access to approved personnel. Records of accountability and storage monitoring (i.e. temperature logs) shall be maintained.

- Maintain records that document adequately that the subjects were provided the doses specified by the protocol and reconcile all investigational product(s) received from the sponsor.
- Explain the correct use of the investigational product(s) to each subject and should check, at intervals appropriate for the trial, that each subject is following the instructions properly.
- A compliance check could include instructing the subjects to return empty and
  partially used containers at their next visit. An assessment would then be
  made of how much medication has been taken versus the expected amount
  of medication to be taken. The compliance check will usually also involve
  asking the subject to describe how and when they are taking the medication.

## The investigator(s) should:

- Ensure that the investigational product(s) are used only in accordance with the approved protocol.
- Follow the trial's randomisation procedures, if any, and should ensure that the
  code is broken only in accordance with the protocol. If the trial is blinded, the
  investigator should promptly document and explain to the sponsor any
  premature unblinding (e.g., accidental unblinding, unblinding due to a serious
  adverse event) of the investigational product(s).

## 5. GLOSSARY

## **Delegate**

A person delegated specific but appropriate tasks in relation to the conduct of a clinical trial.

## **Good Clinical Practice (GCP)**

A standard for the design, conduct, performance, monitoring, auditing, recording, analyses, and reporting of clinical trials that provides assurance that the data and reported results are credible and accurate, and that the rights, integrity, and confidentiality of trial subjects are protected.

## **Human Research Ethics Committee (HREC)**

A body which reviews research proposals involving human participants to ensure that they are ethically acceptable and in accordance with relevant standards and guidelines.

The National Statement requires that all research proposals involving human participants be reviewed and approved by an HREC and sets out the requirements for the composition of an HREC.

VMIA SOP No. 005

RECEIPT AND HANDLING OF INVESTIGATIONAL PRODUCT

Version: 1.0 Dated 17 September 2007

## **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.

## **Investigational Product**

A pharmaceutical form of an active ingredient or placebo being tested or used as a reference in a clinical trial, including a product with a marketing authorization when used or assembled (formulated or packaged) in a way different from the approved form, or when used for an unapproved indication, or when used to gain further information about an approved use.

## 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, 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.

## **Protocol**

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

## **Sub Investigator**

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

## 6. REFERENCES

- 1. Note for guidance on Good Clinical Practice (CPMP/ICH/135/96) annotated with TGA comments DSEB, July 2000, sections 4.6 & 4.7 for Investigator Responsibilities.
- 2. Note for guidance on Good Clinical Practice (CPMP/ICH/135/96) annotated with TGA comments DSEB, July 2000, sections 5.12, 5.13 & 5.14 for Sponsor Responsibilities.
- 3. National Statement on Ethical Conduct in Human Research, (2007).
- 4. Australian Code of Good Manufacturing Practice (GMP) Annex 13 Manufacture of investigational medicinal products.

## 7. APPENDICES

Appendix 1: SOP Change Log

Appendix 2: Example IP accountability log

## **DOCUMENT END**

Version: 1.0 Dated 17 September 2007

## **APPENDIX 1: SOP CHANGE LOG**

Version No.	Reason for Issue
1	First issue

Document: VMIA SOP005 Appendix 2

Approval Date: [dd/mmm/yyyy] Implementation Date: [dd/mmm/yyyy]

# Investigational Product (IP) Accountability Record

									or Comme	ved																
		Lot Number:	Expiry Date:	Used IP:			- All returns should be stored in a separate location		If Transaction = RECEIVE or RETURN	Indicate LOCATION received from or returned to																
				ner 🗆 📉			returns should be st	eturns should be str		eturns should be st		eturns should be str		OUT TOTAL												
				⊐/Oth			- All		Balance of used IP	Z																
				Ambient □ / 2-8°C □ / Other □					of IP	TOTAL																
				լbient □			nacy	nacy	nacy	nacy	nacy	пасу		nacy	пасу	пасу	nacy	nacy		Balance of IP	DOUT					
		n:	īt:				nditions he Pharr		_	Z																
		Dosage Form:	Strength / Unit:	Storage Req'ments:		Location:	r the appropriate cor used or returned to t	the appropriate conditions ised or returned to the Pharmacy	or the appropriate co used or returned to	ar the appropriate coused or returned to			Checked by (Initials)													
				Sto		7	ediately stored under		<b>Details</b>	Performed by (Initials)																
:	Details						ensure product is imn I signed off once all th	ensure product is imm signed off once all th	ensure product is imm signed off once all th	nsure product is imme signed off once all the	nsure product is imm signed off once all the	ensure product is imn signed off once all th	ensure product is im d signed off once all tl	ensure product is im d signed off once all t	ensure product is im d signed off once all t	ensure product is imr I signed off once all th	ensure product is imm signed off once all th	ensure product is imm signed off once all the	signed off once all the	Transaction Details	Subject IDENTIFIER					-
	Section 1 – Investigational Product Details	Investigational Product:	Study Protocol Number:	Research Coordinator:	Section 2 -Storage Location Details		orm Notes - Upon receipt to the storage location, ensure product is immediately stored under the appropriate conditions - This record should be completed and signed off once all the IP has been either used or returned to the Phar	Section 3 – Transaction History		Received, Dispensed or Returned	☐Received ☐Balance carried over															
	Section 1 – Ir	Investigatic	Study Proto	Research	Section 2 –St	Room:	Form Notes - Upon rece - This recor	Section 3 – T	Date/Time	Date Time																

nts

Balance carried over to new record □ Accountability Record Complete: Yes □ Research Coordinator (or delegate):

All IP returned (ie. TOTAL Balance is zero)

. ام

## STANDARD OPERATING PROCEDURE

## Title: Informed Consent Procedures and Writing Patient Informed Consent Forms

Document ID: 006	
Version: <insert as="" local="" per="" quality<="" site="" td="" version="" your=""><td>management system&gt;</td></insert>	management system>
Author: <insert approver="" author="" local="" name="" of="" or=""></insert>	
Author Signature:	Date: <insert date=""></insert>
Effective Date: <insert date="" department="" effe="" is="" procedure="" that="" this=""></insert>	ective from in your institution/
Review Before: <insert date="" of="" procedure="" s<="" td="" this="" when=""><td>hould be reviewed&gt;</td></insert>	hould be reviewed>
Department/institution name: < insert Department/ins	stitution name>
Reviewed and Approved by: <insert name=""></insert>	<insert position="" title=""></insert>
Signature:	Date: <insert date=""></insert>
Departmental Head: < insert name>	
Signature:	Date: <insert date=""></insert>

VMIA SOP No. 006

INFORMED CONSENT PROCEDURES AND WRITING PATIENT INFORMED CONSENT FORMS

Version: 1.0 Dated 17 September 2007

## 1. AIM

To describe the procedures related to informed consent procedures and writing patient informed consent forms.

## 2. SCOPE

All phases of clinical investigation of medicinal products, medical devices diagnostics and therapeutic interventions.

## 3. APPLICABILITY

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

## 4. PROCEDURE

## 4.1 Informed consent procedures

## The investigator(s) should:

- Comply with local HREC requirements, NHMRC National Statement on Ethical Conduct in Human Research (2007) and other applicable regulatory requirement(s), and adhere to GCP and to the ethical principles that have their origin in the Declaration of Helsinki.
- Obtain the HREC's written approval/favourable opinion of the written informed consent form and any other written information to be provided to subjects prior to the beginning of the trial.
- Ensure that the written informed consent form and any other written information to be provided to subjects is revised whenever important new information becomes available that may be relevant to the subject's consent.
- Obtain the HREC's approval/favourable opinion in advance of use for any revised written informed consent form, and written information.
- Ensure the person or persons taking the informed consent have an adequate understanding of the trial and of the informed consent process.
- Inform the subject or the subject's legally acceptable representative in a timely manner if new information becomes available that may be relevant to the subject's willingness to continue participation in the trial. The communication of this information should be documented.
- Not, nor permit trial staff to coerce or unduly influence a subject to participate or to continue to participate in a trial.

- Permit any of the oral and written information concerning the trial, including
  the written informed consent form, to contain any language that causes the
  subject or the subject's legally acceptable representative to waive or to
  appear to waive any legal rights, or that releases or appears to release the
  investigator, the institution, the sponsor, or their agents from liability for
  negligence.
- (Or a person designated by the investigator), fully inform the subject or, if the subject is unable to provide informed consent, the subject's legally acceptable representative, of all pertinent aspects of the trial including the written information and the approval/ favourable opinion by the HREC.
- Ensure that language used in the oral and written information about the trial, including the written informed consent form is as non-technical as practical and should be understandable to the subject or the subject's legally acceptable representative and the impartial witness, where applicable.
- Ensure that before informed consent is obtained, they, or a person designated by the investigator, provide the subject or the subject's legally acceptable representative ample time and opportunity to inquire about details of the trial and to decide whether or not to participate in the trial. All questions about the trial should be answered to the satisfaction of the subject or the subject's legally acceptable representative.
- Ensure prior to a subject's participation in the trial, that the written informed consent form is signed and personally dated by the subject or by the subject's legally acceptable representative, and by the person who conducted the informed consent discussion.
- Ensure if a subject is unable to read or if a legally acceptable representative
  is unable to read, that an impartial witness be present during the entire
  informed consent discussion, and that discussion be held in an appropriate
  language.
- Ensure that after the written informed consent form and any other written
  information to be provided to subjects, is read and explained to the subject or
  the subject's legally acceptable representative, and after the subject or the
  subject's legally acceptable representative has orally consented to the
  subject's participation in the trial and, if capable of doing so, has signed and
  personally dated the informed consent form, the witness should sign and
  personally date the consent form.
- Ensure prior to participation in the trial, the subject or the subject's legally acceptable representative receive a copy of the signed and dated written informed consent form and any other written information provided to the subjects.

- Ensure during a subject's participation in the trial, the subject or their legally acceptable representative receive a copy of the signed and dated consent form updates and a copy of any amendments to the written information provided to subjects.
- Ensure that when a clinical trial (therapeutic or non-therapeutic) includes subjects who can only be enrolled in the trial with the consent of the subject's legally acceptable representative (e.g., minors, or patients with severe dementia), the subject is informed about the trial to the extent compatible with the subject's understanding and, if capable, the subject should sign and personally date the written informed consent.
- Ensure that (except as described immediately below), a non-therapeutic trial (i.e. a trial in which there is no anticipated direct clinical benefit to the subject), is conducted in subjects who personally give consent and who sign and date the written informed consent form.

Note: Non-therapeutic trials may be conducted in subjects with consent of a legally acceptable representative provided the following conditions are fulfilled:

- a. The objectives of the trial can not be met by means of a trial in subjects who can give informed consent personally.
- b. The foreseeable risks to the subjects are low.
- c. The negative impact on the subject's well-being is minimized and low.
- d. The trial is not prohibited by law.
- e. The approval/favourable opinion of the HREC is expressly sought on the inclusion of such subjects, and the written approval/ favourable opinion covers this aspect.

## The investigator(s) should ensure:

- That such trials, unless an exception is justified, are conducted in patients having a disease or condition for which the investigational product is intended. Subjects in these trials should be particularly closely monitored and should be withdrawn if they appear to be unduly distressed.
- That in emergency situations, when prior consent of the subject is not possible, the consent of the subject's legally acceptable representative, if present, is requested. When prior consent of the subject is not possible, and the subject's legally acceptable representative is not available, enrolment of the subject should require measures described in the protocol and/or elsewhere, with documented approval/favourable opinion by the HREC, to protect the rights, safety and well-being of the subject and to ensure compliance with applicable regulatory requirements.

 That the subject or the subject's legally acceptable representative are informed about the trial as soon as possible and consent to continue and other consent as appropriate should be requested.

Please refer to the *National Statement on Ethical Conduct in Human Research*, 2007 for details on obtaining consent in special cases.

## 4.2 Writing patient informed consent forms

## The investigator(s) should:

- Ensure the written informed consent form and any other written information provided to subjects include explanations of the following:
  - a. That the trial involves research.
  - b. The purpose of the trial.
  - c. The trial treatment(s) and the probability for random assignment to each treatment.
  - d. The trial procedures to be followed, including all invasive procedures.
  - e. The subject's responsibilities.
  - f. Those aspects of the trial that are experimental.
  - g. The reasonably foreseeable risks or inconveniences to the subject and, when applicable, to an embryo, foetus, or nursing infant.
  - h. The reasonably expected benefits. When there is no intended clinical benefit to the subject, the subject should be made aware of this.
  - i. The alternative procedure(s) or course(s) of treatment that may be available to the subject, and their important potential benefits and risks.
  - j. The compensation and/or treatment available to the subject in the event of trial related injury.
  - k. The anticipated prorated payment, if any, to the subject for participating in the trial.
  - I. The anticipated expenses, if any, to the subject for participating in the trial.
  - m. That the subject's participation in the trial is voluntary and that the subject may refuse to participate or withdraw from the trial, at any time, without penalty or loss of benefits to which the subject is otherwise entitled.

- n. That the monitor(s), the auditor(s), the HREC, and the regulatory authority(ies) will be granted direct access to the subject's original medical records for verification of clinical trial procedures and/or data, without violating the confidentiality of the subject, to the extent permitted by the applicable laws and regulations and that, by signing a written informed consent form, the subject or the subject's legally acceptable representative is authorizing such access.
- o. That records identifying the subject will be kept confidential and, to the extent permitted by the applicable laws and/or regulations, will not be made publicly available. If the results of the trial are published, the subject's identity will remain confidential.
- p. That the subject or the subject's legally acceptable representative will be informed in a timely manner if information becomes available that may be relevant to the subject's willingness to continue participation in the trial.
- q. The person(s) to contact for further information regarding the trial and the rights of trial subjects, and whom to contact in the event of trial-related injury.
- r. The foreseeable circumstances and/or reasons under which the subject's participation in the trial may be terminated.
- s. The expected duration of the subject's participation in the trial.
- t. The approximate number of subjects involved in the trial.

## 4.3 Training Records

## The investigator(s) should:

- Ensure that all persons assisting with the trial are adequately informed about the protocol, the investigational product(s), and their trial-related duties and functions.
- Ensure that documentation of this training be kept current and available for review on request.

## 5. GLOSSARY

## **Delegate**

A person delegated specific but appropriate tasks in relation to the conduct of a clinical trial.

## **Good Clinical Practice (GCP)**

A standard for the design, conduct, performance, monitoring, auditing, recording, analyses, and reporting of clinical trials that provides assurance that the data and reported results are credible and accurate, and that the rights, integrity, and confidentiality of trial subjects are protected.

## **Human Research Ethics Committee (HREC)**

A body which reviews research proposals involving human participants to ensure that they are ethically acceptable and in accordance with relevant standards and guidelines.

The National Statement requires that all research proposals involving human participants be reviewed and approved by an HREC and sets out the requirements for the composition of an HREC.

## **Informed Consent**

A process by which a subject voluntarily confirms his or her willingness to participate in a particular trial, after having been informed of all aspects of the trial that are relevant to the subject's decision to participate. Informed consent is documented by means of a written, signed and dated informed consent form.

## 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, 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.

## **Protocol**

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

## **Sub Investigator**

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

## 6. REFERENCES

- 1. Note for guidance on Good Clinical Practice (CPMP/ICH/135/96) annotated with TGA comments DSEB, July 2000, sections 4.
- 2. National Statement on Ethical Conduct in Human Research, (2007).

## 7. APPENDICES

Appendix 1: SOP Change Log.

## **DOCUMENT END**

## **APPENDIX 1: SOP CHANGE LOG**

Version No.	Reason for Issue
1	First issue

## STANDARD OPERATING PROCEDURE

## Title : Case Report Forms, Source Documents, Record Keeping and Archiving

Document ID: 007				
Version: <insert as="" local="" per="" quality<="" site="" td="" version="" your=""><td>management system&gt;</td></insert>	management system>			
Author: <insert approver="" author="" local="" name="" of="" or=""></insert>				
Author Signature:	Date: <insert date=""></insert>			
Effective Date: <insert date="" effe<br="" is="" procedure="" that="" this="">department&gt;</insert>	ective from in your institution/			
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Department/institution name: < insert Department/ins	stitution name>			
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Signature:	Date: <insert date=""></insert>			
Departmental Head: < insert name>				
Signature:	Date: <insert date=""></insert>			

## 1. AIM

To describe the procedures related to the completion of case report forms, source documents, record keeping and archiving.

## 2. SCOPE

Applicable to all phases of clinical investigation of medicinal products, medical devices, diagnostics and therapeutic interventions.

## 3. APPLICABILITY

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

## 4. PROCEDURE

## 4.1 Completion of case report forms

## The investigator(s)/ institution should:

- Ensure the accuracy, completeness, legibility, and timeliness of the data reported to the sponsor in the CRFs and in all required reports.
- Ensure that data reported on the CRF, that are derived from source documents, be consistent with the source documents or the discrepancies should be explained.
- Ensure that any change or correction to a CRF is dated, initialled, and explained (if necessary) and should not obscure the original entry (i.e. an audit trail should be maintained); this applies to both written and electronic changes or corrections.
- · Retain records of the changes and corrections.

## 4.2 Source documents, record keeping and archiving

## The investigator(s) should:

- Keep original source documents (where the data was first recorded) and take measures to prevent accidental or premature destruction of these documents.
- Maintain the trial documents as specified in VMIA SOP 002 appendix 1 The Study Site Master File and Essential Documents and as required by the applicable regulatory requirement(s) and take measures to prevent accidental or premature destruction of these documents.

- Ensure that financial aspects of the trial are documented in an agreement between the sponsor and the investigator/institution.
- Ensure that upon request of the monitor, auditor, HREC, or regulatory authority, make available for direct access all requested trial related records.
- Study documentation should be maintained for a minimum of 15 years for adult studies or 25 years for paediatric studies.
- For legal reasons, sites may consider indefinite archiving periods.
- The TGA position on document retention states:

"The TGA requires records to be retained by the sponsor for 15 years following the completion of a clinical trial. However, in Australia the overriding consideration for sponsors with respect to record retention is the issue of product liability and the potential need for sponsors of products to produce records at any time during, and possibly beyond, the life of a product in the event of a claim against the sponsor as a result of an adverse outcome associated with the use of the product"

ICH-GCP requirements for record retention state:

"Ensure that essential documents are retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents should be retained for a longer period however if required by the applicable regulatory requirements or by an agreement with the sponsor".

 Original documents should be retained, scanned copies are not yet generally accepted as archives.

## 5. GLOSSARY

## **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 trial subject.

## **Good Clinical Practice (GCP)**

A standard for the design, conduct, performance, monitoring, auditing, recording, analyses, and reporting of clinical trials that provides assurance that the data and reported results are credible and accurate, and that the rights, integrity, and confidentiality of trial subjects are protected.

## **Human Research Ethics Committee (HREC)**

VMIA SOP No. 007

CASE REPORT FORMS, SOURCE DOCUMENTS, RECORD KEEPING AND ARCHIVING

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, 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.

## **Source Documents**

Original documents (where the data was first recorded), data, and records (e.g., hospital records, clinical and office charts,

laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate copies, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories and at medico-technical departments involved in the clinical trial).

## **Sub Investigator**

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

## 6. REFERENCES

1. Note for guidance on Good Clinical Practice (CPMP/ICH/135/96) annotated with TGA comments DSEB, July 2000, section 4.

## 7. APPENDICES

Appendix 1: SOP Change Log

Appendix 2: Example data corrections

## **DOCUMENT END**

## **APPENDIX 1: SOP CHANGE LOG**

Version No.	Reason for Issue
1	First issue

## Error Correction

S N

jumped over the moon







The conjumped ove the moon.



ped ove the moon.

## Error Correction

COW

John Howard 13~Feb-2007 Incorrect animal.



# The big jumped over the moon.

- Draw a single line through the incorrect entry
- Do not cancel, erase or obscure recorded data
- Explain correction (if not obvious why the correction has been made)
- Make correction
- Sign and date the correction
- White out / liquid paper or pencil must never be used (Only Black Pen)

## STANDARD OPERATING PROCEDURE

Title : Site Initiation and Close-Out				
Document ID: 008				
Version: <insert as="" local="" per="" site<="" td="" version="" your=""><td>quality management system&gt;</td></insert>	quality management system>			
Author: <insert appro-<="" author="" local="" name="" of="" or="" td=""><td>ver&gt;</td></insert>	ver>			
Author Signature:	Date: <insert date=""></insert>			
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Department/institution name: < insert Department	ment/institution name>			
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Signature:	Date: <insert date=""></insert>			
Departmental Head: < insert name>				
Signature:	Date: <insert date=""></insert>			

VMIA SOP No. 008

SITE INITIATION AND CLOSE-OUT

## 1. AIM

To describe the procedures related to site initiation and close-out of a clinical trial.

## 2. SCOPE

Applicable to all phases of clinical investigation of medicinal products, medical devices and diagnostics.

## 3. APPLICABILITY

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

## 4. PROCEDURE

## 4.1 Site initiation

The procedure outlined below refers to a "sponsored" study. Where the investigational study is "investigator initiated" and the "sponsor" is the institution, the investigator should undertake both investigator and monitor roles unless an external monitor has been assigned by the institution.

## Prior to initiation the investigator(s) should:

- Arrange with the monitor the scheduled date, time and location of the study initiation visit.
- Review the Investigator's Brochure and any up-to-date information on the investigational product. The Investigator(s) must be familiar with the product, including pre-clinical toxicology, pharmacology, pharmacokinetics and up-todate clinical data if applicable.
- Ensure that the procedures stated in the study protocol are applicable in their centre and fully understood.
- Ensure that sub Investigator(s), pharmacist(s), research coordinators and any other relevant staff involved with the study have been advised of the meeting and are able to attend.

## During the initiation the investigator(s) or delegate should:

- Establish that the Investigator's Site Mater File contains all the required regulatory documents.
- Provide a list of study personnel and functions in the study to the clinical monitor.

- Provide curricula vitae of the sub Investigators involved.
- Ensure that the names and contact numbers of the relevant medical and study personnel of the sponsor are available and documented clearly.
- Ensure that all relevant study site personnel fill out the Site Personnel/Signature Log.
- Check that the procedures and plans for storage, dispensing and return of investigational product have been agreed and finalised with the Sponsor and Pharmacist (if applicable).
- Review the documents used in the shipment of the investigational products to the study site.
- Check that the quantity of CRFs that have been requested or shipped to the study site are sufficient for the number of subjects/patients that are likely to be recruited into the study.
- Check that other related supplies are available, or are to be shipped to the study site at a later date, and that they are available in sufficient quantities.
- Check that laboratory facilities and arrangements for the dispatch of samples
  to the laboratory are organised and that any specialised equipment that may
  be required will be available throughout the period of the trial, e.g. centrifuge
  freezer, etc.
- Establish who will be responsible for CRF completion and clarify the procedure for entering data in the CRF, as well as making changes and corrections.
- Ensure an understanding of the requirements that source documents and raw data will need to be available during monitoring visits to enable the monitor to perform source data verification at each monitoring visit.
- Review the arrangements for organising and maintaining study files.
- Ascertain that the procedures relating to the archiving of study records at the end of the study is agreeable to the sponsor.
- Establish the next monitoring visit with the Monitor.

# 4.2 Premature Termination or Suspension of a Trial

If the trial is prematurely terminated or suspended for any reason, the investigator/institution should:

• Promptly inform the trial subjects, should assure appropriate therapy and follow-up for the subjects, and, where required by the applicable regulatory requirement(s), should inform the regulatory authority(ies).

#### In addition:

# If the investigator terminates or suspends a trial without prior agreement of the sponsor, the investigator should:

- Inform the institution where applicable, and the investigator/institution should promptly inform the sponsor and the HREC.
- Provide the sponsor and the HREC with a detailed written explanation of the termination or suspension.

# If the sponsor terminates or suspends a trial, the investigator should:

 Promptly inform the institution where applicable and the investigator/institution should promptly inform the HREC and provide the HREC a detailed written explanation of the termination or suspension.

# If the HREC terminates or suspends its approval/favourable opinion of a trial the investigator should:

• Inform the institution where applicable and the investigator/ institution should promptly notify the sponsor and provide the sponsor with a detailed written explanation of the termination or suspension.

#### 4.3 Site close-out

# The investigator(s) should:

- Provide a summary report of the trial's outcome to the ethics committee and the regulatory authorities, if required.
- Keep documentation and correspondence in the trial master file in accordance with 8.4 ICH.
- Inform the sponsor of the completion of the study.
- Ensure arrangements for archiving of trial documents are clarified (see section 6 of VMIA SOP 007).
- Ensure appropriate final disposition of any investigational product. This may include return to the sponsor or destruction of remaining materials. Refer to VMIA SOP 005 for details.

# 5. GLOSSARY

# **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 trial subject.

# **Delegate**

A person delegated specific but appropriate tasks in relation to the conduct of a clinical trial.

# **Good Clinical Practice (GCP)**

A standard for the design, conduct, performance, monitoring, auditing, recording, analyses, and reporting of clinical trials that provides assurance that the data and reported results are credible and accurate, and that the rights, integrity, and confidentiality of trial subjects are protected.

# **Human Research Ethics Committee (HREC)**

A body which reviews research proposals involving human participants to ensure that they are ethically acceptable and in accordance with relevant standards and guidelines.

The National Statement requires that all research proposals involving human participants be reviewed and approved by an HREC and sets out the requirements for the composition of an HREC.

# International 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, 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 initiated trial

A clinical trial that is undertaken by the investigator whereby the investigator and/or their institution takes on the role of the sponsor in addition to their role as investigator.

# Monitoring

The act of overseeing the progress of a clinical trial and ensuring that it is conducted, recorded, and reported in accordance with the protocol, Standard Operating Procedures (SOPs), Good Clinical Practice (GCP), and the applicable regulatory requirement(s).

# **Sponsor**

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

#### **Source Documents**

Original documents, data, and records (e.g., hospital records, clinical and office charts,

laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate copies, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories and at medico-technical departments involved in the clinical trial).

# **Sub Investigator**

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

# 6. REFERENCES

- 1. Note for guidance on Good Clinical Practice (CPMP/ICH/135/96) annotated with TGA comments DSEB, July 2000, sections 4 and 8.4.
- 2. Standard Operating Procedures for Clinical Investigators, World Health Organisation, version 1.1.

#### 7. APPENDICES

Appendix 1: SOP Change Log

Appendix 2: Example Initiation check-list Appendix 3: Example Close out check-list

# **DOCUMENT END**

# **APPENDIX 1: SOP CHANGE LOG**

Version No.	Reason for Issue
1	First issue

# **APPENDIX 2: INITIATION CHECK-LIST**

ACTIVITY		
Ensure the meeting is scheduled and all relevant staff are able to attend (Investigator, study coordinator, sponsor, pharmacist, other relevant people such as laboratory staff). It is usual to confirm the initiation by letter		
Review Investigational Product overview and background		
Review with investigator and relevant staff their understanding of the protocol, study procedures, investigational product, randomization procedures, unblinding procedures and timelines		
Review that site resources are adequate to conduct the trial		
Review with investigator and relevant staff Safety Reporting procedures and principles of Good Clinical Practice (ICH-GCP), including informed consent procedures, investigator responsibilities, record keeping and ethics reporting.		
Review contents of Site Master File to ensure that:		
the current <u>approved</u> copy of the protocol, Informed consent form & Investigational Brochure are present and align with the ethics committee approval documentation		
the ethics approval documentation is present and signed		
a copy of the CTN/CTX form is present and complete		
all necessary agreements are present and signed ( Clinical trial Agreement, Indemnities, insurance)		
all site staff CVs are present and signed		
Laboratory normal ranges and relevant accreditation are present		
Complete staff delegations log		
Review investigational product shipment records		

VMIA SOP No. 008

SITE INITIATION AND CLOSE-OUT

# **APPENDIX 3: CLOSE-OUT CHECK LIST**

ACTIVITY	COMPLETE
Ensure all protocol required data has been collected	
Finalise accountability and disposition of test drug	
Verify that all study files are complete (see Study Master File checklist)	
Discuss overall study conduct at the site	
Collect final signatures for any data queries, signature logs or reports	
Discuss archiving of original data and documents	
Dispose of or return any remaining trial specific supplies	
Formally close the site	

VMIA SOP No. 008

SITE INITIATION AND CLOSE-OUT

Version: 1.0 Dated 17 September 2007

# STANDARD OPERATING PROCEDURE

Title: TGA Notification and SAE Reporting Requirements		
Date: <insert date=""></insert>		
titution name>		
<insert position="" title=""></insert>		
Date: <insert date=""></insert>		
Date: <insert date=""></insert>		

#### 1. AIM

To describe the procedures related to the notification of the TGA and SAE reporting requirements.

#### 2. SCOPE

Applicable to all phases of clinical investigation of medicinal products, medical devices, therapeutic interventions and diagnostics.

#### 3. APPLICABILITY

Principal Investigator, Sub-Investigator, research coordinators and other staff delegated trial-related activities by the Principal Investigator.

#### 4. PROCEDURE

# 4.1 TGA Notification and SAE Reporting Requirements

Note: The document "Access to Unapproved Therapeutic Goods- Clinical trials in Australia October 2004" gives clear direction to sponsor responsibilities which may need to be considered if an investigator is acting in the capacity of a sponsor.

The clinical investigator has a responsibility to ensure the conduct of the trial, including the monitoring of safety and reporting of adverse outcomes, complies with the study protocol. In the case of an investigator initiated study, the investigator must complete the sponsor section of the CTN form.

The sponsor and the principal investigator should review the adverse outcome in the context of known information on the medicine and make a determination as to whether the event was drug-related (i.e. an adverse reaction).

# The investigator(s) should:

- Report immediately (within 24 hours of learning of the event) to the sponsor (or the TGA if an Investigator Initiated Trial) all serious adverse events (SAEs) except for those SAEs that the protocol or other document (e.g., Investigator's Brochure) identifies as not needing immediate reporting. (ADRAC Blue Card or equivalent should be used to report to the TGA). The immediate reports should be followed promptly by detailed, written reports.
- Ensure that the immediate and follow-up reports identify subjects by unique code numbers assigned to the trial subjects rather than by the subjects' names, personal identification numbers, and/or addresses.

Page 2 of 10

- Comply with the applicable regulatory requirement(s) related to the reporting
  of unexpected serious adverse drug reactions to the regulatory authority(ies)
  and the HREC.
- Ensure that adverse events and/or laboratory abnormalities identified in the
  protocol as critical to safety evaluations are reported to the sponsor according
  to the reporting requirements and within the time periods specified by the
  sponsor in the protocol.
- Ensure that for reported deaths, supply the sponsor and the HREC with any additional requested information (e.g., autopsy reports and terminal medical reports).
- Record non-serious and expected adverse reactions and adverse events as part of GCP. It is imperative that, in accordance with GCP principles, an internal statistical analysis of these data is performed. The TGA should be advised of any safety issues which emerge during this process. Such data do not need to be submitted on a routine basis to the TGA during the trial, but should be available for submission to the TGA on request, and where applicable, submitted as part of an application for registration.

# The investigator(s) must:

- notify the institutional ethics committee of SAEs, in line with institutional procedures and as per any specific ethics approval conditions related to the particular study
- notify the HREC of any information received from the sponsor that may be new and have an impact on the continued ethical acceptability of the trial, or may indicate the need for amendments to the trial protocol, including monitoring of safety.

# 5. GLOSSARY

# **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.

Page 3 of 10

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.

# **Good Clinical Practice (GCP)**

A standard for the design, conduct, performance, monitoring, auditing, recording, analyses, and reporting of clinical trials that provides assurance that the data and reported results are credible and accurate, and that the rights, integrity, and confidentiality of trial subjects are protected.

# **Human Research Ethics Committee (HREC)**

A body which reviews research proposals involving human participants to ensure that they are ethically acceptable and in accordance with relevant standards and guidelines.

VMIA SOP No. 009

TGA NOTIFICATION AND SAE REPORTING REQUIREMENTS

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 ensuring 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.

# **Serious Adverse Device Event (SADE)**

A device-related serious adverse event.

# Serious Adverse Event (SAE) - drug

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 patient 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 in-patient hospitalisation or prolongation of existing hospitalisation;
- d. results in persistent or significant disability/incapacity; or
- e. is a congenital anomaly/birth defect, and fits the SAE criteria as specified in the relevant clinical trial protocol.

Medical or scientific judgment 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 subject or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These should also usually be considered serious. Examples of such events are 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 drug abuse.

# Serious Adverse Event (SAE) - device

Serious Adverse Event for *medical devices*: any adverse medical occurrence that:

- a. Led to a death.
- b. Led to a serious deterioration in health of a patient user or other. This would include:
  - a life threatening illness or injury
  - a permanent impairment of body function or permanent damage to a body structure
  - a condition requiring hospitalisation or increased length of existing hospitalisation
  - a condition requiring unnecessary medical or surgical intervention e) foetal distress, foetal death or a congenital abnormality/birth defect
- c. Might have led to a death or a serious deterioration in health had suitable action or intervention not taken place.

# This includes:

- a malfunction of a device such that it has to be modified or temporarily/permanently taken out of service
- a factor (a deterioration in characteristics or performance) found on examination of the device.

Page 6 of 10

# Co Investigator

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

# **Therapeutic Goods Administration (TGA)**

Australia's regulatory agency for medical drugs and devices.

#### 6. REFERENCES

1. ICH E6 Guidelines for Good Clinical Practice, section 4.

VMIA SOP No. 009

TGA NOTIFICATION AND SAE REPORTING REQUIREMENTS

2. Access to Unapproved Therapeutic Goods - Clinical trials in Australia October 2004.

#### 7. **APPENDICES**

Appendix 1: Appendix 2:

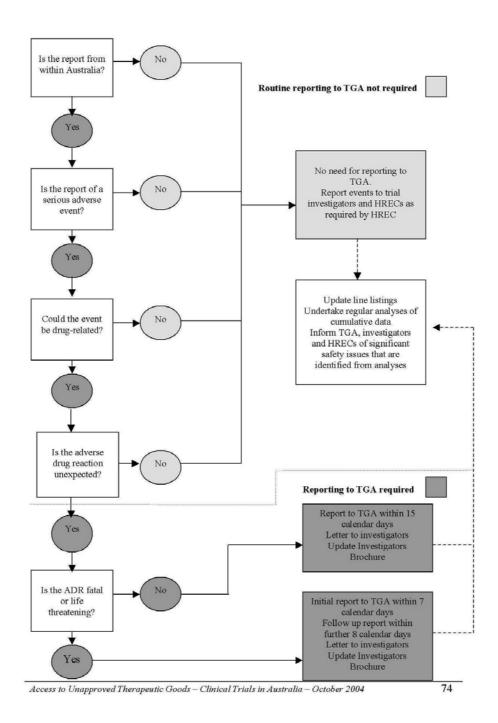
Clinical trial event reporting algorithm for sponsors Reporting requirements for clinical trials conducted under the CTN and

CTX schemes

SOP Change Log Appendix 3:

# **DOCUMENT END**

# APPENDIX 1 : CLINICAL TRIAL EVENT REPORTING ALGORITHM FOR SPONSORS



VMIA SOP No. 009

# TGA NOTIFICATION AND SAE REPORTING REQUIREMENTS

Version: 1.0 Dated 17 September 2007

# APPENDIX 2: REPORTING REQUIREMENTS FOR CLINICAL TRIALS CONDUCTED UNDER THE CTN AND CTX SCHEMES

Reporter	→ Reports what?	→ To whom?	→In what format?	→ In what timeframe?
Sponsor of trial	Serious and unexpected adverse drug reactions		ADRAC blue card <sup>\$</sup>	For fatal or life-threatening ADRs, send initial report within 7 calendar days of first knowledge. Follow up with complete report within 8 additional calendar days.
				For all other serious and unexpected ADRs, full report no later than 15 calendar days of first knowledge by the sponsor.
	Other reactions and adverse events	TGA	Tabulation	On request by TGA.
Clinical	Adverse reactions/even	HREC	As required by HREC	As required by HREC
investigator(s)	Adverse reactions/events	Sponsor of trial	As per study protocol	As per study protocol

<sup>\*</sup> Report should be clearly marked 'Clinical trial ADR' and sent to:

The Medical Adviser Experimental Drugs Section Drug Safety and Evaluation Branch Therapeutic Goods Administration PO Box 100 WODEN ACT 2606

\$ Or an appropriate format that contains the same information

Source: Access to Unapproved Therapeutic Goods – Clinical Trials in Australia, October 2004

Page 9 of 10

VMIA SOP No. 009

TGA NOTIFICATION AND SAE REPORTING REQUIREMENTS

# **APPENDIX 3: SOP CHANGE LOG**

Version No.	Reason for Issue
1	First issue

# STANDARD OPERATING PROCEDURE

Title : Investigator Responsibilities		
Document ID: 010		
Version: <insert version=""></insert>		
Author: <insert name=""></insert>		
Author Signature:	Date: <insert date=""></insert>	
Effective Date: <insert date=""></insert>		
Review Before: <insert date=""></insert>		
Department/institution name: < insert Department/inst	titution name>	
Reviewed and Approved by: <insert name=""></insert>	<insert position="" title=""></insert>	
Signature:	Date: <insert date=""></insert>	
Departmental Head: < insert name>		
Signature:	Date: <insert date=""></insert>	

VMIA SOP No. 010

**INVESTIGATOR RESPONSIBILITIES** 

#### 1. AIM

To define Investigators' responsibilities and to provide instruction when performing clinical study(ies) under applicable regulatory requirements.

#### 2. SCOPE

All phases of clinical investigation of medicinal products, medical devices, therapeutic interventions and diagnostics.

#### 3. APPLICABILITY

Principal Investigator, Sub-Investigator, research coordinators and other staff delegated trial-related activities by the Principal Investigator.

#### 4. PROCEDURE

# 4.1 Investigator Responsibilities

# The investigator(s):

- Should ensure that clinical studies are carried out according to International Conference on Harmonisation (ICH), regulatory authorities requirements and any other local requirements.
- Should have an understanding that when a trial is sponsored by an agency/pharmaceutical company, they may be requested to follow their procedures in order to comply with company obligations. Agreement between all parties should be discussed before initiating the trial.
- Should ensure that they are appropriately qualified to conduct the trial.
- Should inform the subject's primary physician about the subject's participation
  in the trial if the subject has a primary physician and if the subject agrees to
  the primary physician being informed.

Note: Although a subject is not obliged to give his/her reason(s) for withdrawing prematurely from a trial, the investigator should make a reasonable effort to ascertain the reason(s), while fully respecting the subject's rights.

- Must declare any conflicts of interest, payments etc. from other parties.
- Must maintain a list of any delegated duties with respect to the trial, and the persons and qualifications of those persons to whom the duties are assigned.

- Should be able to demonstrate that adequate subject recruitment is likely to be possible, with necessary time available to conduct the study to GCP requirements, and with adequate facilities and trial staff.
- Must provide medical care to trial participants that is necessary as a result of any adverse events experienced during or following the trial that are related to the trial, and must be responsible for all trial-related medical decisions
- Must possess, prior to trial commencement, a favourable HREC endorsement of trial protocol, patient information and consent documents, recruitment procedures, consent form updates and any other information given to subjects.
- Must present all trial related documents to the HREC for review including the Investigator's Brochure as well as updates.
- Must ensure that the trial is conducted according to the approved protocol.
- Must document any deviation from the protocol for later review.
- Must ensure that no deviation from the protocol occurs without HREC endorsement, unless it is required to prevent imminent harm to participants. If the protocol deviation results in the creation of a "separate and distinct" therapeutic good as defined in section 16 of the Therapeutic Goods Act 1989, a new notification is required for CTN or CTX trials.
- Should ensure a new CTN form is completed, or in the case of CTX a new "notification of intent to conduct clinical trial" form, for any new trial site subsequently added to a study.

Note: CTN forms notified must be **originals.** A copy should be kept in the Trial Master File.

- Must ensure accountability of the investigational product at the trial site(s).
- Must ensure that subjects have made fully informed, written consent, with all trial procedures and risks adequately explained and that the principles and essential elements of Informed consent are up held and included in the information document;
- Should be thoroughly familiar with the appropriate use of the investigational product(s), as described in the protocol, in the current Investigator's Brochure, in the product information and in other information sources provided by the sponsor.

- Should ensure that all persons assisting with the trial are adequately informed about the protocol, the investigational product(s), and their trial-related duties and functions.
- Should submit written summaries of the trial status to the HREC annually, or more frequently, if requested by the HREC.
- Should provide written reports to the sponsor, the HREC and, where applicable, the institution promptly on any changes significantly affecting the conduct of the trial, and/or increasing the risk to subjects.
- Should comply with the applicable regulatory requirement(s) related to the reporting of unexpected serious adverse drug reactions to the regulatory authority(ies) and the HREC.
- Should promptly inform the trial subjects If the trial is prematurely terminated or suspended for any reason as well as the institution and should assure appropriate therapy and follow-up for the subjects, and where required by the applicable regulatory requirement(s), inform the regulatory authority(ies).

Note: if the investigator terminates or suspends a trial without prior agreement of the sponsor, they should inform the institution where applicable, and the investigator/institution should promptly inform the sponsor and the HREC, and provide the sponsor and the HREC a detailed written explanation of the termination or suspension.

 Should, upon completion of the trial, where applicable, inform the institution; the investigator/institution should provide the HREC with a summary of the trial's outcome, and the regulatory authority(ies) with any reports required.

# 5. GLOSSARY

# Adverse event (AE)

Any untoward medical occurrence in a patient administered a medicinal product and which does not necessarily have to have a causal relationship with this treatment. An adverse event can therefore be any unfavourable and unintended sign (for example, an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to this medicinal product.

# **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.

# **Good Clinical Practice (GCP)**

A standard for the design, conduct, performance, monitoring, auditing, recording, analyses, and reporting of clinical trials that provides assurance that the data and

reported results are credible and accurate, and that the rights, integrity, and confidentiality of trial subjects are protected.

# **Human Research Ethics Committee (HREC)**

A body which reviews research proposals involving human participants to ensure that they are ethically acceptable and in accordance with relevant standards and guidelines.

The National Statement requires that all research proposals involving human participants be reviewed and approved by an HREC and sets out the requirements for the composition of an HREC.

# **International 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 ensuring 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.

# Sub Investigator

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

# 6. REFERENCES

- 1. Note for guidance on Good Clinical Practice (CPMP/ICH/135/96) annotated with TGA comments DSEB, July 2000, sections 4.
- 2. Standard Operating Procedures for Clinical Investigators, World Health Organisation, version 1.1.
- 3. The Australian Clinical Trial Handbook, Therapeutic Goods Administration, March 2006.
- 4. Access to Unapproved Therapeutic Goods, Clinical Trials in Australia, Therapeutic Goods Administration, October 2004

#### 7. APPENDICES

Appendix 1: SOP Change Log

#### **DOCUMENT END**

# **APPENDIX 1: SOP CHANGE LOG**

Version No.	Reason for Issue
1	First issue

# STANDARD OPERATING PROCEDURE

Title : Sponsor Responsibilities In Inves	stigator Initiated Studies
Document ID: 011	
Version: <insert version=""></insert>	
Author: <insert name=""></insert>	
Author Signature:	Date: <insert date=""></insert>
Effective Date: <insert date=""></insert>	
Review Before: <insert date=""></insert>	
Department/institution name: < insert Department/inst	titution name>
Reviewed and Approved by: <insert name=""></insert>	<insert position="" title=""></insert>
Signature:	Date: <insert date=""></insert>
Departmental Head: < insert name>	
Signature:	Date: <insert date=""></insert>

#### 1. AIM

To define Sponsor Responsibilities in the conduct of Investigator driven studies.

#### 2. SCOPE

All phases of clinical investigational for medical products, medical devices and diagnostics.

#### 3. APPLICABILITY

Where the Investigator is acting in the capacity of sponsor.

#### 4. PROCEDURE

# 4.1 Sponsor Responsibilities

The sponsor for an investigator initiated study may be an individual (eg the investigator or department head), a company (e.g. a not-for-profit) an organisation (e.g. a charity) or an institution (e.g. a public hospital). Each institutional will have its own policy regarding the sponsorship role.

# The sponsor is responsible for:

- Ensuring that any clinical trial involving a drug or device not approved for marketing in Australia (or approved for an indication other than that proposed in the clinical trial) and for which there is no commercial sponsorship, obtains approval from the VMIA.
- Ensuring that Quality Assurance and Quality Control systems are in place to ensure trials are conducted, data is gathered, and subsequently reported, in compliance with GCP, the trial protocol, and any TGA requirements.
- Securing agreement from all involved parties to ensure direct access to all trial related sites, source data/documents, and reports for the purpose of monitoring and auditing by the sponsor, and inspection by domestic and foreign regulatory authorities.
- Ensuring that no omissions occur which might disentitle themselves, the Hospital or HREC, to such indemnity as could otherwise be available under the Medical Indemnity and Public Liability Policies.
- Selection of the appropriate investigator(s) and institution(s) to conduct and complete the trial according to GCP standards.
- Definitive, unambiguous allocation of trial-related duties and responsibilities to trial-related staff.

- The provision of appropriate insurance and indemnity for the trial and trialrelated staff, as well as measures for subject compensation for trial-related injury.
- Ensuring the confirmation of endorsement from the relevant HREC(s) and notification of the approval etc. to the TGA.
- Ensuring that funding arrangements are declared in the protocol submissions to warrant that the clinical trial retains its "investigator initiated" status under the VMIA policy.
- Ensuring medical expertise is on hand for trial-related medical queries or patient care.
- Trial design and appropriate analysis.
- Data handling, record keeping, and overall trial management.
- Must maintain all records relating to the study for a period of at least 15 years from the end of the Trial (i.e. completion of data analysis) in the case of adults and at least 25 years from the end of the Trial (i.e. completion of data analysis) in the case of children.
- Ensuring that agreements made with the investigator/institution and any other
  parties involved with the clinical trial, are in writing, as part of the protocol or
  in a separate agreement.
- Ensuring that Investigational Products available to subjects free of charge.
- Taking appropriate urgent safety measures (with investigator) where necessary.
- Keeping records of all adverse events reported by investigators.
- Ensuring appropriate manufacture, packaging, labelling/coding and distribution to trial sites of all investigational medicinal products.
- Ongoing safety evaluation and AE/ADR reporting as described earlier in this document.
- Compliance with Monitoring/Audit/Inspection requirements.
- Notification of any premature termination of the trial in question.
- Completion of the Clinical Study Report.

# 5. GLOSSARY

# Adverse drug reaction (ADR)

Adverse drug reactions concern noxious and unintended responses to a medicinal product.

# Adverse event (AE)

Any untoward medical occurrence in a patient administered a medicinal product and which does not necessarily have to have a causal relationship with this treatment. An adverse event can therefore be any unfavourable and unintended sign (for example, an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to this medicinal product.

# **Clinical Trials Agreement (CTA)**

An agreement governing the safety and efficacy of outside collaborators, proprietary biologics or pharmaceutical compounds in clinical studies.

# **European Union (EU)**

An organization of European countries.

# **Good Clinical Practice (GCP)**

A standard for the design, conduct, performance, monitoring, auditing, recording, analyses, and reporting of clinical trials that provides assurance that the data and reported results are credible and accurate, and that the rights, integrity, and confidentiality of trial subjects are protected.

# **Human Research Ethics Committee (HREC)**

A body which reviews research proposals involving human participants to ensure that they are ethically acceptable and in accordance with relevant standards and guidelines.

The National Statement requires that all research proposals involving human participants be reviewed and approved by an HREC and sets out the requirements for the composition of an HREC.

# **International 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 ensuring 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 initiated trial

A clinical trial that has the following characteristics:

- A pharmaceutical/device company is not acting as the sponsor for the purposes of the CTN application.
- A pharmaceutical/device company is not fully funding the conduct of the study, that is, making payment to the relevant hospital or investigator.
- The clinical trial addresses relevant clinical questions and not industry needs.
- The principal investigator or the Hospital/Institution is the primary author and custodian of the clinical trial protocol.

# Serious adverse event (SAE)

Any untoward medical occurrence that at any dose:

- · Results in death.
- Is life-threatening.

(NOTE: The term "life-threatening" in the definition of "serious" refers to an event/reaction in which the patient was at risk of death at the time of the event/reaction; it does not refer to an event/ reaction which hypothetically might have caused death if it were more severe).

- Requires inpatient hospitalisation or results in prolongation of existing hospitalisation.
- Results in persistent or significant disability/incapacity.
- Is a congenital anomaly/birth defect.
- Is a medically important event or reaction.

#### **Sponsor**

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

# **Sub Investigator**

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

# **Therapeutic Goods Administration (TGA)**

Australia's regulatory agency for medical drugs and devices.

# 6. REFERENCES

- 1. Note for guidance on Good Clinical Practice (CPMP/ICH/135/96) annotated with TGA comments DSEB, July 2000, section 5.
- 2. Standard Operating Procedures for Clinical Investigators, World Health Organisation, version 1.1.
- 3. EU Clinical Trials Directive, Sponsorship responsibilities in publicly funded trials, Medicines for Human Use (Clinical Trials) Regulations 2004, section 5.
- 4. The Australian Clinical Trial Handbook, the Therapeutic Goods Administration, March 2006.
- 5. Victorian Managed Insurance Authority Guidelines for Clinical Trials for Victorian Public Hospitals, 2006.

#### 7. APPENDICES

Appendix 1: SOP Change Log

**DOCUMENT END** 

# **APPENDIX 1: SOP CHANGE LOG**

Version No.	Reason for Issue
1	First issue

# STANDARD OPERATING PROCEDURE

# Title : Handling and Shipping of Infectious Substances for Clinical Trials

10. 0	ioui iiiuio
Document ID: 012	
Version: <insert version=""></insert>	
Author: <insert name=""></insert>	
Author Signature:	Date: <insert date=""></insert>
Effective Date: <insert date=""></insert>	
Review Before: <insert date=""></insert>	
Department/institution name: < insert Department	artment/institution name>
Reviewed and Approved by: <insert name:<="" td=""><td>&gt; <insert position="" title=""></insert></td></insert>	> <insert position="" title=""></insert>
Signature:	Date: <insert date=""></insert>
Departmental Head: < insert name>	
Signature:	Date: <insert date=""></insert>

#### 1. AIM

To outline the correct procedures for the handling and shipping of infectious substances in clinical trials.

#### 2. SCOPE

All phases of clinical investigation for medicinal products, medical devices and diagnostics.

#### 3. APPLICABILITY

Principal Investigator, Sub-Investigator, research coordinators and other staff delegated trial-related activities by the Principal Investigator.

#### 4. PROCEDURE

# 4.1 Handling and Shipping of Infectious Substances for Clinical Trials

# The investigator(s) should:

- Ensure that clinical specimens are handled and packed in accordance with local, sponsor and, if being shipped by air ICAO requirements (see document referenced in section 5). This includes the confirmation that staff involved in packaging and shipping of infectious waste/dangerous goods are appropriately qualified and trained. (Dangerous Goods Handling training courses & certification may be required if this service is not provided by the courier company).
- Identify patient specimens for which there is minimal likelihood that pathogens are present are not subject to the ICAO requirements if the specimen is transported in Packaging for Exempt Patient Specimens.
- In determining whether a patient specimen has a minimal likelihood that pathogens are present, exercise an element of professional judgement. That judgement should be based on the known medical history, symptoms and individual circumstances of the source, human or animal, and endemic local conditions.

Examples of specimens which may be transported as a patient specimen for which there is a minimal likelihood that pathogens are present include:

- blood or urine tests to monitor cholesterol levels, blood glucose levels or hormone levels;
- tests required to monitor organ function such as heart, liver or kidney function for humans with non-infectious diseases:

- therapeutic drug monitoring;
- pregnancy tests;
- biopsies to detect cancer; and
- antibody detection in humans or animals.

Patient specimens (human or animal) that have a minimal likelihood of containing pathogens must be packaged appropriately to further minimize the risk of exposure. While these specimens have a minimal likelihood of containing infectious pathogens in a form that would cause infection, appropriate packaging further minimizes the risk of exposure (see appendix 1).

# 4.2 Tracking of Handling and Shipping of Infectious Substances for Clinical Trials

The investigator/delegate should ensure that documentation related to handling and shipping of infectious substances is maintained and filed to facilitate tracking and to satisfy GCP requirements.

# 5. GLOSSARY

## **Delegate**

A person delegated specific but appropriate tasks in relation to the conduct of a clinical trial.

# **Good Clinical Practice (GCP)**

A standard for the design, conduct, performance, monitoring, auditing, recording, analyses, and reporting of clinical trials that provides assurance that the data and reported results are credible and accurate, and that the rights, integrity, and confidentiality of trial subjects are protected.

# Infectious substances

Those substances which are known to contain, or are reasonably expected to contain, pathogens.

# **International Civil Aviation Organization (ICAO)**

A specialized agency of the United Nations which sets international standards and regulations necessary for the safety, efficiency and regularity of air transport.

# **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 ensuring 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.

# **Medical or clinical wastes**

Those derived from the medical treatment of animals or humans or from bio-research.

# **Pathogens**

Micro-organisms (including bacteria, viruses, rickettsiae, parasites, fungi) and other agents such as prions, which can cause disease in humans or animals.

# **Patient specimens**

Those collected directly from humans or animals, including, but not limited to, excreta, secreta, blood and its components, tissue and tissue fluid swabs, and body parts being transported for purposes such as research, diagnosis, investigational activities, disease treatment and prevention.

#### **Sub Investigator**

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

#### 6. REFERENCES

1. International Civil Aviation Organization Technical Instructions for the Safe Transport of Dangerous Goods by Air, 2005-2006.

#### 7. APPENDICES

Appendix 1: ICAO technical instructions for packaging of exempt human or animal

specimens.

Appendix 2: Example of packing and marking for exempt human specimens or

exempt animal specimens

Appendix 3: SOP Change Log

# **DOCUMENT END**

## APPENDIX 1: ICAO TECHNICAL INSTRUCTIONS FOR PACKAGING OF EXEMPT HUMAN OR ANIMAL SPECIMENS.

Patient specimens (human or animal) that have a minimal likelihood of containing pathogens must be packaged appropriately to further minimize the risk of exposure.

While these specimens have a minimal likelihood of containing infectious pathogens in a form that would cause infection, appropriate packaging further minimizes the risk of exposure.

ICAO Technical Instructions require exempt human or animal specimens to be packaged and marked according to the following:

- i. a leak-proof primary receptacle(s);
- ii. a leak-proof secondary packaging; and
- iii. an outer packaging of adequate strength for its capacity, mass and intended use, and with at least one surface having minimum dimensions of 100 mm × 100 mm;

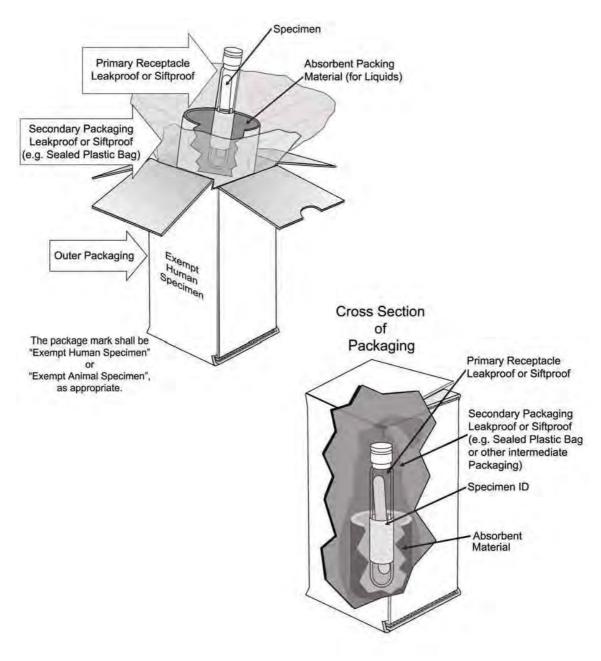
For liquids, absorbent material in sufficient quantity to absorb the entire contents must be placed between the primary receptacle(s) and the secondary packaging so that, during transport, any release or leak of a liquid substance will not reach the outer packaging and will not compromise the integrity of the cushioning material;

When multiple fragile primary receptacles are placed in a single secondary packaging, they must be either individually wrapped or separated to prevent contact between them.

If such a packaging is used it must be marked "Exempt human specimen" or "Exempt animal specimen", as appropriate (see appendix 2 graphic of an Exempt Patient Specimen Packaging).

**Note:** if other dangerous goods are present with patient specimens the relevant provisions of the ICAO technical instructions apply to those goods (see referenced document).

# APPENDIX 2: EXAMPLE OF PACKING AND MARKING FOR EXEMPT HUMAN SPECIMENS OR EXEMPT ANIMAL SPECIMENS



### **APPENDIX 3: SOP CHANGE LOG**

Reason for Issue
First issue

### STANDARD OPERATING PROCEDURE

# Title: Standard Operating Procedure (SOP) Creation, Implementation and Revision

Document ID: 013	
Version: <insert version=""></insert>	
Author: <insert name=""></insert>	
Author Signature:	Date: <insert date=""></insert>
Effective Date: <insert date=""></insert>	
Review Before: <insert date=""></insert>	
Department/institution name: < insert Department/ins	titution name>
Reviewed and Approved by: <insert name=""></insert>	<insert position="" title=""></insert>
Signature:	Date: <insert date=""></insert>
Departmental Head: < insert name>	
Signature:	Date: <insert date=""></insert>

VMIA SOP No. 013

### 1. AIM

To document the procedure for the creation and implementation of new SOP's and review of existing SOP's.

### 2. SCOPE

This applies to all SOP's when a need is identified to either create a new SOP or modify an existing one.

### 3. APPLICABILITY

The designated SOP writer and Investigator/Subinvestigator.

### 4. PROCEDURE

### 4.1 Flow chart

See appendix 1.

### 4.2 Initiating the creation of a new SOP or revision of an existing SOP.

### All staff may:

- Identify the need for a new SOP or a deficiency in an existing SOP.
- Notify the SOP author or QA officer (if applicable) and discuss the need with them.

### The QA officer/document reviewer will:

- Assess and verify the identified need and if appropriate assign a Document ID number to the new SOP or a new version number to a modified SOP.
- Ensure that the provided SOP template in appendix 2 is used for all new SOP's.
- Maintain a Document Register of approved SOPs that includes as a minimum the Document ID, version number, approval date, effective date and review before date.

### 4.3 Preparation of a new SOP or revision of an existing SOP

### The QA officer/document reviewer will:

 For a new SOP, prepare a draft in accordance with the standard SOP Template which includes the following sections:

### VMIA SOP No. 013

- 1. Aim
- 2. Scope
- 3. Applicability [revise order for all SOPs 1,2,3,6,4,5,7]
- 4. Procedure
- 5. Glossary
- 6. References
- 7. Appendices
- Use sub-section numbering (eg 6.1, 6.2, 6.3 etc) as required to keep the document clear and easy to follow.
- For a modified SOP, edit the current version of the SOP.
- Distribute the draft new or modified SOP to the QA officer or the document reviewer for review and comment.
- Incorporate relevant comments and arrange for further review if required.
   Print the final SOP and arrange for approval and authorisation by the QA officer or the document reviewer.

### 4.4 Approval and Authorisation of the SOP

 Prior to the release of the SOP it will be reviewed and approved by QA or delegate and finally authorised by the department head or Institutional delegate.

### 4.5 Assigning 'Effective' and 'Review Before' dates to the SOP

- The SOP effective date shall usually be one calendar month from the date of authorisation. However, the lapsed time between SOP authorisation and the effective date may be reduced in special circumstances (eg urgent situations where procedures must be implemented immediately).
- All relevant staff shall be trained in the new/updated SOP between the authorisation and the effective date
- The Institutional delegate or Investigator shall record the 'Effective Date' on page 1 of the SOP.
- The SOP 'Review Before' date shall be two years from the SOP's assigned "Effective Date".

VMIA SOP No. 013

• The Institutional delegate or Investigator shall record the 'Review Before' date on page 1 of the SOP.

### 4.6 Distribution of the new or revised SOP

- At least one controlled copy will be available for use by the study team. Further copies will also be tracked and controlled (see appendix 4).
- Controlled copies shall be clearly identified.
- The master SOP (ie. with original signatures) shall be securely stored and used only for making further controlled copies if required.
- Controlled versions of SOPs may be made available in an electronic form, such as a .pdf document.

### 4.7 Recall of superseded SOPs

- The document controller will ensure the superseded copies are returned and confidentially destroyed.
- The superseded master SOP shall be clearly marked as superseded and be securely stored as a record of previously used SOPs.

### 5. GLOSSARY

### **Controlled Document**

A document that has been created or modified through a controlled documentation process. Such a document cannot be modified without going through a documented process of change control. A controlled document will have a version number, an approval signature and be dated. In most cases there is a review and authorisation step in addition.

### **Good Clinical Practice (GCP)**

A standard for the design, conduct, performance, monitoring, auditing, recording, analyses, and reporting of clinical trials that provides assurance that the data and reported results are credible and accurate, and that the rights, integrity, and confidentiality of trial subjects are protected.

### **Delegate**

A person delegated specific but appropriate QA tasks in relation to SOP generation.

VMIA SOP No. 013

### **Document controller**

A person responsible for the distribution and maintenance of SOPs.

### **Document reviewer**

A person delegated the task of reviewing SOP's by QA or the Institution or Investigator.

### **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, 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.

### **Quality Assurance Officer (QA)**

In general, the person assigned the task of ensuring overall quality of a range of activities to enhance the quality of a given function or system.

### **Standard Operating Procedure (SOP)**

Detailed, written instructions to achieve uniformity of the performance of a specific function.

### 6. REFERENCES

1. Note for guidance on Good Clinical Practice (CPMP/ICH/135/96) annotated with TGA comments DSEB, July 2000, sections 1 and 5

### 7. APPENDICES

Appendix 1: Flow chart

Appendix 2: Standard SOP Template

Appendix 3: Annotated example of SOP cover page [to be added]

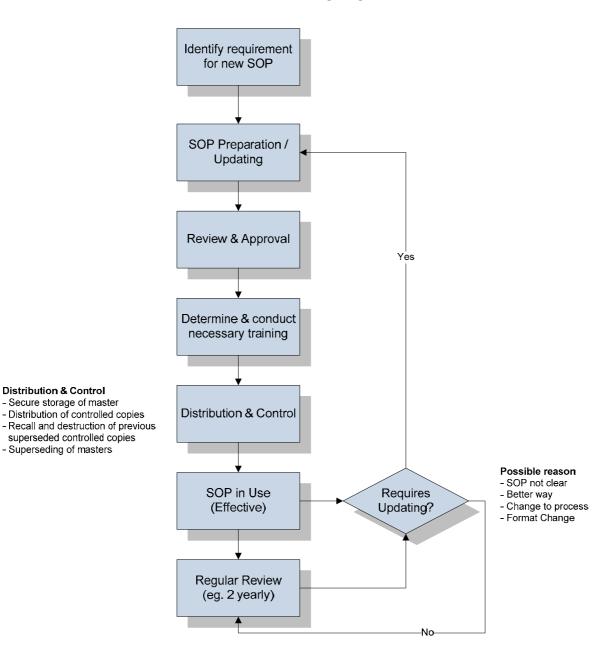
Appendix 3: Document review form Appendix 4: Document tracking form

Appendix 5: SOP Change Log

### **DOCUMENT END**

VMIA SOP No. 013

### **APPENDIX 1: FLOW CHART**



### VMIA SOP No. 013

Distribution & Control - Secure storage of master

superseded controlled copies - Superseding of masters

### **APPENDIX 2: STANDARD SOP TEMPLATE**

Title	:
Document ID: XXX	
Version: <insert version=""></insert>	
Author: <insert name=""></insert>	
Author Signature:	Date: <insert date=""></insert>
Effective Date: <insert date=""></insert>	
Review Before: <insert date=""></insert>	
Site/institution name: < insert Site/institution i	name>
Reviewed and Approved by: <insert name=""></insert>	<insert position="" title=""></insert>
Signature:	Date: <insert date=""></insert>
Principal Investigator: < insert name>	
Signature:	Date: <insert date=""></insert>

VMIA SOP No. 013

TITLE

- 1. AIM
- 2. SCOPE
- 3. APPLICABILITY
- 4. PROCEDURE
  - 4.1 Subheading
  - 4.2 Subheading
- 5. GLOSSARY
- 6. REFERENCES
- 7. APPENDICES

Appendix 1: Appendix title

Appendix (last): SOP Change Log

### **DOCUMENT END**

VMIA SOP No. 013

TITLE

### **APPENDIX X : FLOW CHART (IF APPLICABLE)**

Version No.	Reason for Issue
1	First issue
2	(List changes from previous version)

VMIA SOP No. 013

STANDARD OPERATING PROCEDURE CREATION, IMPLEMENTATION AND REVISION

# **APPENDIX 3 : DOCUMENT REVIEW FORM**

Document Reviewed (Document ID)	Reviewer comments	QA or Second Reviewer Comments

VMIA SOP No. 013

STANDARD OPERATING PROCEDURE CREATION, IMPLEMENTATION AND REVISION

	Destroy (X)		
	Copy Return Destroy no. (X) (X)		
	Copy no.		
	Date sent		
ORM	Copy Return Destroy no. (X) (X)		
KING F	Return (X)		
TRAC	Copy no.		
MENT	Date sent		
NDIX 4: DOCUMENT TRACKING FORM	Return Destroy (X) (X)		
	Return (X)		
APPE	Copy no.		
	Date sent		
	Effective date		
	Documen t ID		

VMIA SOP No. 013

TITLE

### **APPENDIX 5: SOP CHANGE LOG**

Version No.	Reason for Issue
1	First issue

VMIA SOP No. 013

STANDARD OPERATING PROCEDURE CREATION, IMPLEMENTATION AND REVISION