Early Phase Clinical Trials Guidance on the Scientific Expert Review Toolkit

VICTORIA State Government | Department of Health

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Contents

Glossary

(The TGA glossary for definitions to the regulation of therapeutic goods in Australia may change from time to time.)

Active implantable medical device (AIMD)

An active medical device (other than an implantable medical device) that is intended by the manufacturer:

(a) either:

  (i) to be by surgical or medical intervention, introduced wholly, or partially, into the body of a human being; or

  (ii) to be, by medical intervention, introduced into a natural orifice in the body of a human being; and

(b) to remain in place after the procedure

Adverse Device Event (ADE)

Includes events resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, or operation, malfunction of the investigational device, use error, or any intentional misuse of the investigational medical device.

Australian Register of Therapeutic Goods (ARTG)

Maintained under s. 9A of the Therapeutic Goods Act 1989 for the purpose of compiling information in relation to, and providing for evaluation of, therapeutic goods for use in humans.

Australian Sponsor

An Australian Sponsor is a representative appointed by a non-Australian medical device and IVD manufacturer to act as a contact liaison with the Therapeutic Goods Administration (TGA). An Australian Sponsor must be a resident of Australia or maintain a place of business in Australia.

Biological

A thing that comprises, contains, or is derived from human cells or human tissue; and is represented in any way to be, or is likely to be, for therapeutic use.

Biological medicines

Biological medicines are therapeutic goods that are derived from biological sources and are regulated as registered medicines. Biological medicines are distinct from 'biologicals' which are human cell and tissue products.

Clinical Research Organisation CRO

A service organisation that provides support to the pharmaceutical and biotechnology industries. CROs offer client a wide range of "outsourced" pharmaceutical research services to aid in the drug and medical device research and development process.

Clinical Trial (synonyms: clinical study, intervention study)

A planned study in humans of an intervention (including a medicine, treatment or diagnostic procedure) with the object of investigating safety or efficacy and designed to achieve at least one of the following: the discovery or verification of clinical, pharmacological or other pharmacodynamic effects; the identification of adverse reactions or adverse effects; the study of absorption, distribution, metabolism or excretion.

Clinical Trial Sponsor

The Clinical Trial Sponsor is responsible for the safety of subjects in a clinical trial and informs local site investigators of the true historical safety record of the drug, device or other medical treatment to be tested, and of any potential interactions of the study treatment(s) with already approved medical treatments.

CTN

Clinical Trial Notification scheme

CTA

Clinical Trial Approval scheme (previously named Clinical Trial Exemption CTX)

Early phase trials

Broadly defined as non-therapeutic, exploratory trials in human participants who may be healthy volunteers or have a specific disease.

Essential principles

The essential principles set out the requirements relating to the safety and performance characteristics of medical devices (see the Australian Regulatory Guidelines for Medical Devices)

GMP clearance

The approval of GMP documentary evidence that shows a manufacturer is of an acceptable standard

Good clinical practice (GCP)

A standard for the design, conduct, performance, monitoring, auditing, recording, analysis 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.

Good laboratory practice (GLP)

A set of quality standards defining the organisational processed and the conditions under which nonclinical studies (i.e. those not conducted in humans *in vivo*) are planned, performed, monitored, recorded, archived and reported. This is to provide assurance of the reliability of results obtained from safety-related studies performed in animals and *in vitro*.

Good manufacturing practice (GMP)

The acronym GMP is used internationally to describe a set of principles and procedures which, when followed by manufacturers of therapeutic goods, helps ensure that the products manufactured will have the required quality. A basic tenet of GMP is that quality cannot be tested into a batch of product but must be built into each batch of product during all stages of the manufacturing process.

HREC

Human Research Ethics Committee review research proposals involving human participants to ensure that they are ethically acceptable and in accordance with relevant standards and guidelines.

Informed consent

In relation to treatment or proposed treatment, means consent freely given by a person on the basis of information concerning the potential risks and benefits of the treatment that was sufficient information to allow the person to make an informed decision whether to consent to the treatment.

IVD or IVDD

In vitro diagnostic device

Medicine

A therapeutic goods (other than biologicals) that are represented to achieve, or are likely to achieve, their principal intended action by pharmacological, chemical, immunological or metabolic means in or on the body of a human; and any other therapeutic goods declared by the Secretary, for the purpose of the definition of therapeutic device, not to be therapeutic devices.

Medical Device

(a) any instrument, apparatus, appliance, material or other article (whether used alone or in combination, and including the software necessary for its proper application) intended, by the

person under whose name it is or is to be supplied, to be used for human beings for the purpose of one or more of the following:

(i) diagnosis, prevention, monitoring, treatment or alleviation of disease;

(ii) diagnosis, monitoring, treatment, alleviation of or compensation for an injury or handicap;

(iii) investigation, replacement or modification of the anatomy or of a physiological process;

(iv) control of conception;

and that does not achieve its principal intended action in or on the human body by pharmacological, immunological or metabolic means, but that may be assisted in its function by such means; or

(b) an accessory to such an instrument, apparatus, appliance, material or other article.

OGTR

Office of Gene Technology Regulator

RMP

Risk management plan

Therapeutic Goods Administration (TGA)

The TGA is a division of the Australian Government Department of Health and is responsible for regulating biologicals, medicines and medical devices.

Unapproved therapeutic goods

An unapproved therapeutic good for the purposes of the CTN and CTA schemes includes:

- any medicine not included in the Australian Register of Therapeutic Goods (ARTG), such as any new formulation, strength or size, dosage form, name, indications, directions for use or type of container of a medicine already in the ARTG
- any medical device (including an in vitro diagnostic device (IVD)) not included in the ARTG, such as any new sponsor, manufacturer, device nomenclature system code, classification or unique product identifier (for certain classes of medical devices only) of a medical device already in the ARTG
  - any in-house IVD medical device, used for the purpose of a clinical trial, where the laboratory providing the in-house IVD is unable to comply with the regulatory requirements for in-house IVDs
- any biological not included in the ARTG such as:
  - any new applicable standards, intended clinical use or principal manufacturer of a Class 1 or 2 biological already in the ARTG
  - any new product name, dosage form, formulation or composition, therapeutic indication, type of container or principal manufacturer of a Class 3 or 4 biological already in the ARTG
- therapeutic goods already included in the ARTG to be used in a manner not covered by the existing entry in the ARTG.

Purpose

This document provides background information and guidance for a scientific expert reviewer to conduct scientific review, at the request of an ethics committee in Victoria, regarding early phase clinical trials. Early phase trials are described in the TGA *Australian clinical trial handbook* (March 2018) as non-therapeutic, exploratory trials in human participants who may be healthy volunteers or have a specific disease.

A review 'toolkit' has been developed containing proforma templates designed to inform the ethics committee regarding scientific aspects of the trial for their deliberation. Other relevant application documents would include: Investigator Brochure; Protocol; Risk Management Plan; Participant Information and Consent Form/s; Investigational Product information; and other relevant information.

The National Statement on Ethical Conduct in Human Research (NHMRC 2007) (National Statement) requires each institution to be satisfied that human research meets ethical and scientific standards. An important aspect of this assurance is evidence of peer scientific review of a research protocol.

The HREC may seek the advice of an external or internal Scientific Expert Reviewer on any aspect of an early phase clinical trial application which is higher risk and may be beyond the expertise of its' Committee members. Scientific Expert Review is intended to support and supplement quality and safety decision making in the ethics review process.

Clinical trials and the regulation of 'unapproved' therapeutic goods

Clinical trials are conducted for new therapeutic goods and trials contribute to the data and information provided by the sponsor to the Therapeutic Goods Administration (TGA) when applying for inclusion of a 'good' on the Australian Register of Therapeutic Goods (ARTG), for use in Australia and for access to treat patients.

The TGA *Australian clinical trial handbook*, *August 2021*, Australian Clinical Trial Handbook describes the requirements and responsibilities of an ethics committee to review clinical trials of unapproved therapeutic goods before a clinical trial can commence. The TGA administers two schemes that allow for the importation into and/or supply in Australia of 'unapproved' therapeutic goods for use in a clinical trial. These are the Clinical Trial Notification (CTN) and Clinical Trial Approval (CTA) schemes. The CTN scheme is used for various phases for a drug (e.g. Phase III, Phase IV), medical device (e.g. pivotal study, post-market study) and bioavailability/bioequivalence clinical trials for medicines and biologicals. The CTN scheme can be used for early phase clinical trials if an ethics committee can access adequate expert scientific and clinical review. Otherwise, the CTA scheme is available for high risk studies or novel treatments such as gene therapy. CTA may be mandatory for certain products. For medical device trials the CTA scheme should be considered where the experimental device involves elements that have not been previously evaluated in clinical trials.

The Australian Clinical Trial Handbook provides information for ethics committees on when the use of the CTN or CTA schemes may be appropriate.

Types of therapeutic goods

The Therapeutic Goods Administration uses a risk management approach to classifying medicines, medical devices and biological products.

Medicines

The TGA Handbook defines a medicine as follows:

(a) *therapeutic goods (other than biologicals) that are represented to achieve, or are likely to achieve, their principal intended action by pharmacological, chemical, immunological or metabolic means in or on the body of a human; and*

(b) *any other therapeutic goods declared by the Secretary, for the purpose of the definition of therapeutic device, not to be therapeutic devices*

For further definitions and examples see the TGA website and the TGA Australian Clinical Trial Handbook under 'Types of therapeutic goods page 7'. The Secretary (Therapeutic Goods Administration) may declare a therapeutic good and definitions may change from time to time.

Medical Devices

Medical devices are classified by the TGA according to intended purpose and risk. The classification rules are prescribed in Schedule 2 and 2A of the *Therapeutic Goods (Medical Devices) Regulations 2002*. Refer to the TGA Australian Clinical Trial Handbook page 8 for definition of a medical device.

The classification of clinical trial stages of a medical device uses a set of rules based on:
the manufacturer's intended use of the device, level of risk to patients, users and other persons (the probability of occurrence of harm and the severity of that harm), degree of invasiveness in the human body and duration of use.

For further information on the classification of IVDs is available on the TGA website. Medical Devices & IVDs l TGA

Biologicals

A Biological is a product made from, or that contains, human cells or human tissues, or live animal cells, tissues or organs and that is used to:

- treat or prevent disease, ailment, defect or injury
- diagnose a condition of a person
- alter the physiological processes of a person
- test the susceptibility of a person to disease
- replace or modify a person's body parts

Products that fall under this definition can be:

1. Regulated as biologicals under the biologicals regulatory framework
2. Not regulated as therapeutic goods (excluded)

3. Regulated as therapeutic goods, but not as biologicals

For further information refer to TGA Australian Clinical Trial Handbook page 9 and the *Australian regulatory guidelines for biologicals (ARGB)*

Biologicals are classified by the Therapeutic Goods Administration into four risk-based classes according to the level of risk posed. Class 3 and Class 4 biologicals are prepared using more complex methods. Class 3 has the potential to alter the cells or tissue and the biological properties. Class 4 have been modified to artificially introduce a function. Some products may be specified as Class 4 for another reason to which both of the following paragraphs apply:

- the biologicals comprise, contain or are derived from human cells or human tissues that have been modified to artificially introduce a function or functions of the cells or tissues
- the artificially introduced function or functions were not intrinsic to the cells or tissues when they were collected from the donor.

Table 4: Classification of Biologicals

Class	Level of Manipulation	Risk	Examples
Class 3	Prepared using more complex methods, methods or for a non-homologous use	medium	demineralised bone, cultured fibroblasts for skin repair, chondrocytes for cartilage repair
Class 4	Cells have been modified to artificially introduce a function, or are pluripotent stem cells	high	genetically modified cells, such as chimeric antigen receptor expressing cells, pluripotent stem cells

Biological medicines are distinct from 'Biologicals' which include goods that comprise or contain live animal cells, tissues or organs.

Early phase trials of Class 4 biologicals must normally be conducted under the CTA scheme. However, where there is sufficient safety information available, it may be possible to use the CTN scheme. Advice should be sought from the TGA if it is believed the CTN route could be used.

Further information is available from the Therapeutic Goods Administration Australian Clinical Trial Handbook.

Clinical trial phases and stages

Clinical trials of medicines and biologicals typically proceed through 'phases' of development whereas clinical trials of medical devices are more appropriately represented by ‘stages’. The tables below provide a summary and comparison of the phases and stages of clinical trials involving the use of therapeutic goods.

Table 5: Summary of clinical trial phases for medicines and biologicals

Phase	Indicative number of participants	Objectives
Phase 0: Human pharmacology (micro-dosing)	10-15 Involves dosing a limited number of humans with a limited range of doses for a limited period of time	**Assess pharmacokinetics** Gather preliminary data on pharmacokinetics and bioavailability to determine if the drug behaves as expected from preclinical studies 'Micro-dosing' studies
Phase I: Human pharmacology	10-100 May involve the first administration to humans, usually to small numbers of healthy volunteers or to patients	**Safety and tolerance** Define or describe pharmacokinetics and pharmacodynamics Determine dosing Explore drug metabolism and drug interactions Identify preferred routes of administration Phase Ia: Single ascending dose Phase Ib: Multiple ascending dose
Phase II: Therapeutic exploratory	100-300 May be undertaken in a larger group of human patients (several hundred)	**Efficacy and safety** Phase IIa: Demonstrate clinical efficacy or biological activity through pilot studies Explore therapeutic dose range Phase IIb: Determine optimum therapeutic dose and regimen (with efficacy as primary endpoint) Resolve uncertainties regarding the design and conduct of subsequent trials
Phase III: Therapeutic confirmatory	300-3000 Usually involve a large group of patients (from several hundred to several thousand)	**Safety, efficacy or effectiveness** Phase IIIa: Determine the therapeutic effect in patient populations for which the drug is eventually intended Provide a definitive assessment of risk-benefit balance (to support drug registration or change in clinical practice) Phase IIIb: Increase patient exposure and support marketing claims or publication

Phase	Indicative number of participants	Objectives
Phase IV: Therapeutic use	1000's	**Post marketing surveillance or resolution of treatment uncertainties** Monitor safety in real world populations To refine knowledge of the risk-benefit balance, detect rare or long-term adverse effects, drug interactions Pharmacoeconomics to gather data in support of the use Comparative effectiveness and community based research (sometimes described as Phase V trials) Trial combinations with existing products

Table 6: Summary of clinical trial stages for medical devices

Stage	Indicative number of participants	Objectives
Pre-market pilot	10-30 Usually involves a small group of human patients	Exploratory investigations to determine preliminary safety and performance information to plan design modifications or provide support for a future pivotal study. (Includes first in human and feasibility studies or proof of concept)
Pre-market pivotal	100's	Confirmatory investigations to evaluate performance and safety for a specified intended use to satisfy pre-market regulatory requirements
Post-market	1000's	Confirmatory investigations to establish performance and safety, for example, in broader populations OR Observational investigations or surveillance to gain better understanding of device safety, long-term outcomes, health economics

Early phase trials

Early phase trials are no longer defined as traditional Phase I trials. Early phase trials can be broadly defined as non-therapeutic, exploratory trials in human participants who may be healthy volunteers or have a specific disease.

Early phase trials combine a number of different study parts within an integrated trial protocol. Common activities and objectives of early phase clinical trials using integrated trial protocols (human pharmacology) are outlined in the table below.

Table 7: Early phase clinical trials using integrated trial protocols (human pharmacology)

Initial studies	Follow-up studies
• Single dose in increasing amounts • Basic safety, tolerability and pharmacokinetics (PK) Possibly pharmacodynamics (PD)	• Repeat dose studies over longer periods of time – Single ascending dose (SAD) – Multiple ascending dose (MAD) • Influences of food and other drugs on PK or PD • Influences of renal and liver impairment on PK • Specific suspected toxicities (for example, heart rhythm)

Similar activities and objectives may be applied to early phase trials for biologicals, with additional consideration of the potential risk posed by the biological to patients, medical personnel and the population as a result of the origin of the cells or tissue, the manufacturing process, or the route of administration. Additional aspects of integrated trial protocols may include:

- requirement for concomitant medication, for example immunosuppressive regimens, for effect
- monitoring of viability, proliferation or differentiation, migration and persistence
- specific potential toxicities (for example, immune responses, infections, malignant transformation)

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Scientific Expert Reviewer

Review Proformas

Early phase clinical trials involving new technologies have increased the diversity of science and engineering of new therapeutic goods and need to focus on more specific and discipline appropriate expert review of research applications.

Four specific Scientific Expert Review Proformas and two Supplementary Review Proformas are designed to assist in assessment of the content of the research application information for sufficiency of evidence, assessment of risk, safety and soundness of the science.

An expert reviewer should use any of the four proformas, depending on the therapeutic good being used in the clinical trial. Some trials may require multiple proformas depending on the study product (e.g. combination drug and medical device trial).

Scientific Review Proformas

- Toxicology
- Medicines
- Medical Devices
- Biologicals

The **Supplementary Review Proformas** are focussed on key scientific aspects and should be used as applicable to the type of clinical trial being reviewed.

- Biodynamics and Kinetics
- Immunology

More than one proforma may be required e.g. a device trial with a biological component.

Therapeutic good categories

Medicines

In general, consideration should be given but not limited to the following:

- Does the Investigator Brochure describe the rationale to determine the dose (e.g. animal models, in vitro data), route of administration, duration of treatment and monitoring?
- Has pharmacokinetic information been provided in the Investigator Brochure?
- Does the protocol adequately describe and conform to the treatment protocol in relation to the intended mode of use/treatment regime.
- For use of an unapproved therapeutic product or new uses of an existing therapeutic good, is there a clear justification and consideration of the nature of the condition being treated and availability of alternative treatments?
- Have risks associated with administration of a therapeutic product and its expected safety effects been addressed in a Risk Management Plan?
- Are toxicology studies adequate according to the ICH M3 Guidelines?

Medical devices

Given the intrinsic risk of early phase device trials, special consideration should be given to the following aspects.

(i) Safety

- Have the risks associated with substances that may ingress and/or egress out of the device been minimised?
- Has the control of infection and contamination; animal, microbial, tissue derivatives and other substances been adequately addressed by the manufacturer?
- Has the minimisation of exposure to radiation, where applicable, been adequately addressed?
- Have other environmental risks been noted and minimised and adequately explained?
- Has the use of a device with other materials, other accessories or in combination with other devices been adequately addressed?

(ii) Compliance

- Has the Unique Product Identifier been incorporated in the investigational product information, manufacturer's instructions for use, protocol and patient information?
- Has the issue of traceability been adequately addressed?
- Has the manufacturer adequately addressed accuracy, precision and the stability of measurements for the long term for a device that has a measurement function?
- Is there assurance for a device or in vitro diagnostic device regarding regularity of maintenance and calibration in accordance with the manufacturer's instructions?

Biologicals

Biological products and methods of manipulation of cells can be very diverse and therefore protocols for clinical trials may also be variable. Some of the possible considerations that may arise in assessing the scientific, safety and risks of using biological products are indicated below.

(i) Biodynamics and kinetics

- Biodynamic properties: functional tests, details of structural or histological assays and assessments of compatibility, degradation rates and functionality where a non-cellular component is combined with a human cell-based product.
- Biokinetic properties: methods for assessing viability, proliferation/differentiation, body distribution/migration and functionality. The expected in vivo life span of the product throughout the whole administration schedule should be considered.
- Persistence studies demonstrating tissue distribution, viability, trafficking, growth and phenotype and any alteration of phenotype due to factors in the body's environment.
- Interaction and integration of the Biological with the applied tissue/cells or its surrounding tissue together with the non-cellular structural components and other bioactive molecules.

Some specific questions are listed below for consideration, as applicable.

- Have animal models been used to demonstrate any undesirable physiological effects of the biological including bioactive products?

- Has safety pharmacology been considered? Depending on the product, for example, cells may secrete a pharmacologically active substance.
- Have kinetics of migration and persistence studies been performed to demonstrate tissue distribution, viability, trafficking, growth, phenotype and alterations of phenotype due to factors in the body's environment?
- Is there sufficient information provided regarding cell-based products that may produce systemically active molecules? Has the distribution, duration and amount of expression of these molecules, the survival and functional stability of the cells at target sites been investigated in animal or other models?
- Has the interaction of the biological good with surrounding cells and tissues been examined?
- If the biological has effects related to cell deficiency or destruction of cells or tissues are there functional tests required?
- If there is lifelong treatment to restore or replace cells or tissues, has testing for functionality to confirm the presence of the cells been described?
- Has the expected in vivo life span of the human cell-based product been addressed, to inform multiple administration of cells?
- If there is a non-cellular component combined with a human cell-based product has the combination been assessed clinically for compatibility, degradation rate and functionality?
- For human cell-based products, is the methodology adequate for monitoring viability, proliferation/differentiation, body distribution/migration and functionality during the period of use?

(ii) Clinical safety and efficacy

- Have all safety issues from the pre-clinical development stage been addressed? Is there an animal model or another predictive approach?
- For human cell-based biologicals, has the likelihood of an immune response, infections, malignant transformation and concomitant treatment been addressed?
- For treatments with long-term viability is there a plan for participant follow-up and surveillance of long-term efficacy and safety issues?
- Are there clinically meaningful endpoints identified for the therapeutic treatment?
- Will the duration of the therapeutic effect of the product be evaluated?

(iii) Toxicology

- Has toxicology applicable to a single and repeated dose been assessed?
- Is the biological likely to have genotoxic effects?
- Is there a risk of developmental and reproductive toxicity?
- Are there altered cellular physiology properties associated with use of the biological?
- Is there a risk of proliferation of the applied cells in an unwanted quantity and /or in an unwanted location?
- Have effects such as immunogenicity, auto-immunity and tumourigenesis been assessed?
- Are there likely to be target organs for toxicity?

(iv) Dose finding studies

- For an individual dose has the body environment and cell mass density been determined and tested in a confirmatory trial for example, first time in human and/or evidence from other phase I/II studies?
- Has a Safe Maximal Dose been determined (without unacceptable adverse effects) and considered where repeated administration schedules are used?

Investigators and Sponsors

General considerations

The ethics application documentation should address but is not be limited to the following guidance:

- Is there sufficient evidence demonstrating compliance with the International Committee on Harmonization-Good Clinical Practice (ICH GCP) including how the clinical trial is to be monitored?
- Is there adequate content in the application that describes quality assurance systems including Standard Operating Procedures (SOPs) to guide the clinical investigation team?
- Does the application provide specific procedural documentation of the oversight requirements of Principal Investigators, institutional sponsors and regulatory authorities relating to the conduct of the clinical trial?
- Are the risks associated with participation in the trial adequately explained in the Participant Information and Consent Form?
- Is there sufficient evidence in the application to support the risk and benefit of conducting a clinical trial?
- A detailed Risk Management Plan is required for all early phase trials.
- Is there adequate detail in the scientific information provided and is this in keeping with Australian guidance?
- Is there adequate detail encompassing the safety monitoring requirements of regulatory agencies for both Australian and multinational clinical trials?
- Is there adequate content in the application that describes the methods by which safety issues are identified and managed?
- Have all known and likely risks and safety of participants been identified and an explanation of risk mitigation provided
- Is there satisfactory detail regarding the identification and monitoring process for adverse events including the reporting requirements to HRECs, sponsors and regulatory authorities for both Australian and multinational clinical trials?

Safety issues and risk mitigation

The scientific expert review information relates to drug, biological and medical devices trials. Scientific Expert Review proformas are provided for these types of trials, recognising there may be common elements. The toolkit also includes review supplements for Biodynamics and Kinetics, and Immunology.

The Scientific Expert Review may be performed according to the toolkit proformas and the sponsor and investigator should be familiar with the approach of the toolkit. The outcome of the expert scientific review will be provided to the ethics committee as part of the documentation for their deliberation.

Clinical trials for unapproved therapeutic goods may arise from a large commercial company and trial data used for inclusion of the ‘good’ on the Australian Register of Therapeutic Goods.

Other trials may be institution sponsored and initiated by either an individual investigator or by an institution. Such trials may be for inclusion purposes or may involve use of a registered good but used for a different indication.

The following is a guide on some of the important aspects that should be addressed in the clinical trial ethics application documentation and the following should be noted:

- Treatment Strategy: including dosing intervals, availability of supportive treatments and emergency care. Such information should be presented in a Risk Management Plan.
- Risk Management Plan: risk identification and risk mitigation.
- Monitoring Safety Plan: surveillance and parameters defined for adverse events or adverse reactions and the reporting of such events to the HREC, by the Sponsor and other study sites.

Risk Management Plan

In early phase clinical trials, the safety and well-being of trial participants and trial staff should always be the priority. There should be special consideration to risk identification and the development of a framework for effective risk mitigation; to be determined early and prior to the protocol being finalised.

Risks whether they are identified or are a potential should be considered at a system level (e.g. facilities, personnel, SOPs) and at the trial level (e.g. the Investigational Product, trial design and data collection).

Risks can also arise from the protocol and study procedures themselves, such as clinical procedures specified by the protocol therefore should be factored in to the risk identification and mitigation process.

For each risk identified, an appropriate mitigation strategy should be implemented, or a determination made that the risk can be accepted. A Risk Management Plan should include the following:

(i) *Risk identification and evaluation*

- Risk identification and evaluation is the key to managing and mitigating risks. A risk evaluation process covers the assessment of the likelihood of potential hazards associated with the trial and the extent to which such hazards would be detectable. This should identify data integrity, safety of study participants and personnel.
- Clinical trial facilities should be assessed against all aspects of the trial. The following should be included: trial design, dosing regimens; stopping criteria; exposure; predictable reactions; emergency treatments; access to facilities for the treatment of medical emergencies; and any additional and/or specialist staffing and training.
- Identify adverse events and/or laboratory abnormalities that are critical to safety evaluations and required expedited reporting from the investigator to the sponsor and noted in the protocol.
- Administrative and ethical considerations should include informed consent, insurance coverage, safety reporting, monitoring, data management and computer systems, traceability of investigational products, clinical sample management and analysis.

(ii) Risk control

- The purpose of risk control is to reduce the risk to an acceptable level or determine that the risk can be accepted. The main components of risk control are risk mitigation, adaptations and risk acceptance actions.
- The risk assessment and risk mitigation should involve multiple functionalities and cover all aspects of the trial. Various personnel may be involved in risk control such as data managers, statisticians, trial managers, monitors, pharmacists and research nurses.

- Procedures, documents and manuals should clearly address risk mitigation (e.g. Standard Operating Procedures, pharmacy manuals, training materials, parameters used for site selection and contractual quality agreements).

(iii) Risk review

- Risks should be assessed as new information emerges during the conduct of the trial. This may include: new preclinical trial data; new safety data; protocol amendments; and DSMB meeting outcomes. This ongoing risk review may impact the risk assessment and mitigation strategy.

(iv) Risk communication

- There should be a process to communicate to the relevant personnel any risk assessment, mitigation plan, as well as changes that may impact on the conduct of the trial (e.g. serious breaches and safety reporting).

(v) Risk reporting

- In accordance with Good Clinical Practice the sponsor should describe the implemented risk adaptations in the risk management plan.

(vi) Long term monitoring

- Special consideration should be given to potential long-term consequences on physiological systems and long-term safety, if delayed or ongoing unexpected adverse events are caused by the investigational product. The length of the monitoring period within and outside the research site should be justified to the ethics committee as part of the treatment strategy to manage risks in the clinical trial. It may be necessary to implement long-term follow-up for study participants after finalisation of the study.

Specific considerations in preparing applications for medicine, medical device and biological clinical trials

Medicines

Early phase clinical trials may involve the first administration of a medicine to humans, usually to small numbers of healthy volunteers. Where this a new chemical entity, it is critical that nonclinical studies (performed in animals and *in vitro*) provide evidence to support that the starting dose in humans is acceptably safe. Phase I clinical trials determine the safety of the medicine, how it works and how well it is tolerated. Clinical trials also identify preferred routes of administration (e.g. tablet, liquid or injection) and help determine the appropriate dose/s for later studies.

Some DNA vaccines are excluded from regulation under the *Gene Technology Act, 2000*. If a vaccine is encapsulated in a lipid coat or other nanoparticle, it is subject to regulation under the *Gene Technology Act 2000* and a licence from the Gene Technology Regulator is required. Additional information can be found on the Office of the Gene Technology Regulator website at: www.ogtr.gov.au

Drug information

Consideration should be given to the following:

- Does the Investigator Brochure describe the rationale to determine the dose (e.g. animal models, in vitro data), route of administration, duration of treatment and monitoring?
- Has pharmacokinetic information been provided in the Investigator Brochure?
- Does the protocol adequately describe and conform to the treatment protocol in relation to the intended mode of use/treatment regime.
- For use of an unapproved therapeutic product or new uses of an existing therapeutic good, is there a clear justification and consideration of the nature of the condition being treated and availability of alternative treatments?
- Have risks associated with administration of a therapeutic product and its expected safety effects been addressed in a Risk Management Plan?

Medical Devices

Given the intrinsic risk of early phase device trials, special consideration should also be given to the following aspects:

(i) Safety

- Have the risks associated with substances that may ingress and/or egress out of the device been minimised?
- Has the control of infection and contamination; animal, microbial, tissue derivatives and other substances been adequately addressed by the manufacturer?
- Has the minimisation of exposure to radiation, where applicable, been adequately addressed?
- Have other environmental risks been noted and minimised and adequately explained?
- Has the use of a device with other materials, other accessories or in combination with other devices been adequately addressed?

(ii) Compliance

- Has the Unique Product Identifier been incorporated in the investigational product information, manufacturer's instructions for use, protocol and patient information?
- Has the issue of traceability been adequately addressed?
- Has the manufacturer adequately addressed accuracy, precision and the stability of measurements for the long term for a device that has a measurement function?
- Is there assurance for a device or In vitro diagnostic device regarding regularity of maintenance and calibration in accordance with the manufacturer's instructions?

Biologicals

A Risk Management Plan (RMP) based on the EMA/CHMP Guideline on Safety and Efficacy follow-up Risk Management of Advanced Therapy Medicinal Products (EMEA/CHMP 149995/2008) should address routine biovigilance and traceability of the biological.

Special long-term studies to monitor specific safety issues must be addressed in a Risk Management Plan (e.g. infections, immunogenicity/immunosuppression, malignant transformations, loss of efficacy, and in vivo durability of any associated medical device/biomaterial component).

Biological goods can be diverse and some of the following questions may or may not apply to assess risk, safety and possible on-target and off-target effects.

(i) Clinical safety

- Have all safety issues from the pre-clinical development stage been addressed? Is there an animal model or another predictive approach?
- For human cell-based biologicals, has the likelihood of an immune response, infections, malignant transformation and concomitant treatment been addressed?
- For treatments with long-term viability is there a plan for participant follow-up and surveillance of long-term efficacy and safety issues?

(ii) Clinical efficacy

- Are there clinical meaningful endpoints identified for the therapeutic treatment?
- Will the duration of the therapeutic effect of the product be evaluated?
- Is there a long-term follow up plan for participants required?

(iii) Dynamics and kinetics

- Have animal models been used to demonstrate any undesirable physiological effects of the biological including bioactive products?
- Has safety pharmacology been considered? Depending on the product, for example, cells may secrete a pharmacologically active substance.
- Have kinetics of migration and persistence studies been performed to demonstrate tissue distribution, viability, trafficking, growth, phenotype and alterations of phenotype due to factors in the body's environment?
- Is there sufficient information provided regarding cell-based products that may produce systemically active molecules? Has the distribution, duration and amount of expression of these molecules, the survival and functional stability of the cells at target sites been investigated in animal or other models?
- Has the interaction of the biological good with surrounding cells and tissues been examined?

(iv) Toxicology

- Has toxicology applicable to a single and repeated dose been assessed?
- Is the biological likely to have genotoxicity effects?
- Is there a risk of developmental and reproductive toxicity?
- Are there altered cellular physiology properties associated with use of the biological?
- Is there a risk of proliferation of applied cells in an unwanted quantity and in an unwanted location?
- Have effects such as immunogenicity, auto-immunity and tumourigenesis been assessed (if applicable)?

(v) Biodynamics

- If the biological has effects related to cell deficiency or destruction of cells or tissues are there functional tests required?

- If there is lifelong treatment to restore or replace cells or tissues, has testing for functionality to confirm the presence of the cells been described?
- If there is a non-cellular component combined with a human cell-based product has the combination been assessed clinically for compatibility, degradation rate and functionality?

(vi) Biokinetics

- For human cell-based products, is the methodology adequate for monitoring viability, proliferation/differentiation, body distribution/migration and functionality during the period of use?
- Has the expected in vivo life span of the human cell-based product been addressed, to inform multiple administration of cells?

(vii) Dose finding studies

- For an individual dose has the body environment and cell mass density been determined and tested in a confirmatory trial for example, first time in human and/or evidence from other phase I/II studies?
- Has a Safe Maximal Dose been determined (without unacceptable adverse effects) and considered where repeated administration schedules are used?

Ethics Committee

General considerations

HREC members should be deliberate on general requirements regarding high risk clinical trials. Some of the considerations may include but would not be limited to the following.

- Are the qualifications of the Investigator and trial staff appropriate?
- Is the safety evaluation of hazards and risks relevant to clinical use?
- Is there adequate detail pertaining to risk mitigation and risk management?
- Are the risks associated with participation adequately conveyed in the Participation Information Consent Form?
- Does the risk management plan adequately address aspects that are highlighted in the scientific expert review regarding safety issues?
- Is the frequency of reporting required by the Sponsor and Principal Investigator adequate?
- Is there sufficiency of evidence to support use in humans?

Considerations specific to the type of clinical trial

Medicines

Early phase clinical trials may involve the first administration of a medicine to humans, usually to small numbers of healthy volunteers. Phase I clinical trials determine the safety of the medicine, how it works and how well it is tolerated. Clinical trials also identify preferred routes of administration (e.g. tablet, liquid or injection) and help determine the appropriate dose/s for later studies.

Some DNA vaccines are excluded from regulation under the *Gene Technology Act, 2000*. If a vaccine is encapsulated in a lipid coat or other nanoparticle, it is subject to regulation under the *Gene Technology Act 2000* and a licence from the Gene Technology Regulator is required. Additional information can be found on the Office of the Gene Technology Regulator website at: www.ogtr.gov.au

Consideration should be given to the following:

- Does the Investigator Brochure describe the rationale to determine the dose (e.g. animal models, in vitro data)**,** route of administration, duration of treatment and monitoring?
- Has pharmacokinetic information been provided in the Investigator Brochure?
- Does the protocol adequately describe and conform to the treatment protocol in relation to the intended mode of use/treatment regime.
- For use of an unapproved therapeutic product or new uses of an existing therapeutic good, is there a clear justification and consideration of the nature of the condition being treated and availability of alternative treatments?
- Have risks associated with administration of a therapeutic product and its expected safety effects been addressed in a Risk Management Plan?
- Are the toxicology studies adequate according to the ICH M3 Guidelines?

Medical Devices

Given the intrinsic risk of early phase device trials, special consideration should be given to the following aspects.

(i) Safety

- Have the risks associated with substances that may ingress and/or egress out of the device been minimised?
- Has the control of infection and contamination; animal, microbial, tissue derivatives and other substances been adequately addressed by the manufacturer?
- Has the minimisation of exposure to radiation, where applicable, been adequately addressed?
- Have other environmental risks been noted and minimised and adequately explained?
- Has the use of a device with other materials, other accessories or in combination with other devices been adequately addressed?

(ii) Compliance

- Has the Unique Product Identifier been incorporated in the investigational product information, manufacturer's instructions for use, protocol and patient information?
- Has the issue of traceability been adequately addressed?
- Has the manufacturer adequately addressed accuracy, precision and the stability of measurements for the long term for a device that has a measurement function?
- Is there assurance for a device or In vitro diagnostic device regarding regularity of maintenance and calibration in accordance with the manufacturer's instructions?

Biologicals

Biological goods can be diverse and some of the following questions may or may not apply to assess risk, safety and possible on-target and off-target effects.

(i) Clinical safety

- Have all safety issues from the pre-clinical development stage been addressed? Is there an animal model or another predictive approach?
- For human cell-based biologicals, has the likelihood of an immune response, infections, malignant transformation and concomitant treatment been addressed?
- For treatments with long-term viability is there a plan for participant follow-up and surveillance of long-term efficacy and safety issues?

(ii) Clinical efficacy

- Are there clinical meaningful endpoints identified for the therapeutic treatment?
- Will the duration of the therapeutic effect of the product be evaluated?
- Is there a long-term follow up plan for participants required?

(iii) Dynamics and kinetics

- Have animal models been used to demonstrate any undesirable physiological effects of the biological including bioactive products?
- Has safety pharmacology been considered? Depending on the product, for example, cells may secrete a pharmacologically active substance
- Have kinetics of migration and persistence studies been performed to demonstrate tissue distribution, viability, trafficking, growth, phenotype and alterations of phenotype due to factors in the body's environment?
- Is there sufficient information provided regarding cell-based products that may produce systemically active molecules? Has the distribution, duration and amount of expression of these molecules, the survival and functional stability of the cells at target sites been investigated in animal or other models?
- Has the interaction of the biological good with surrounding cells and tissues been examined?

(iv) Toxicology

- Has toxicology applicable to a single and repeated dose been assessed?
- Is the biological likely to have genotoxicity effects?
- Is there a risk of developmental and reproductive toxicity?
- Are there altered cellular physiology properties associated with use of the biological?
- Is there a risk of proliferation of applied cells in an unwanted quantity and in an unwanted location?
- Have effects such as immunogenicity, auto-immunity and tumourigenesis been assessed (if applicable)?

(v) Biodynamics

- If the biological has effects related to cell deficiency or destruction of cells or tissues are there functional tests required?
- If there is lifelong treatment to restore or replace cells or tissues has testing for functionality to confirm the presence of the cells been described?
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(vi) Biokinetics

- For human cell-based products, is the methodology adequate for monitoring viability, proliferation/differentiation, body distribution/migration and functionality during the period of use?
- Has the expected in vivo life span of the human cell-based product been addressed, to inform multiple administration of cells?

(vii) Dose finding studies

- For an individual dose has the body environment and cell mass density been determined and tested in a confirmatory trial for example, first time in human and/or evidence from other phase I/II studies?
- Has a Safe Maximal Dose been determined (without unacceptable adverse effects) and considered where repeated administration schedules are used?

Overview and example of a new biological treatment approach and clinical trials

Advances in using biological agents has initiated new therapies involving immunotherapy and an example of this is adoptive cell transfer involving collection of a patient's own immune cells, genetically engineering the cells and infusing them back into the patient. One of these therapies is the chimeric antigen receptor T-cell (often referred to as CAR T-cell) technology involving genetic modification of cells for therapy with a biological product.

Chimeric antigen receptor clinical trials have involved different T-cell genetic domain modifications being tested in children and adults. Early studies focussed on acute lymphocytic leukaemia in children and modification of the CD19 domains in T-cells. The CD19 antigen, associated with B cells, accounts for 80 per cent of paediatric acute lymphocytic leukaemias. A high rate of complete response was achieved in early clinical trials. Subsequently larger trials using CD19-targeted chimeric antigen receptor technology have been conducted in children and adults.

Regulatory approval for this biological therapy has been gained from the European Medicines Agency for acute lymphocytic leukaemia and for relapsed and refractory diffuse large B-cell lymphoma. The United States Food and Drug Administration has also granted regulatory approval in paediatric acute lymphocytic leukemia. Regulatory approval is being sought in other jurisdictions including Australia.

Chimeric antigen receptor therapies using different genetic modifications have offered promising data and possibility of treatment for previously untreatable conditions. However, there are side effects and sometimes fatal outcomes using this therapeutic approach. Side-effects may be general for this therapy approach or may be linked to the types of genetic modification and the domain type used for targeting cancer cellular antigens.

Some of the side effects observed include:

- Cytokine-release syndrome where a rapid and massive release of cytokines occur in the bloodstream leading to very high fevers and large drop in blood pressure. This is an 'on-target' effect of chimeric antigen receptor T-cell therapy and generally occurs in participants with extensive disease. Supportive therapies are used to manage this side-effect, including steroids and anti-inflammatory drugs to counteract high IL-6 levels.
- An 'off-target' effect is B-cell aplasia (massive death of B-cells) due to CD19 being expressed on normal B-cells and this is treated with immunoglobulin therapy to boost antibodies and counteract infections.
- Cerebral oedema has been observed in some clinical trials and is a potential fatal side effect observed in participants with advanced leukaemias and some trials have been halted.
- Neurotoxicities have been observed in most chimeric antigen receptor T-cell therapy trials and include confusion and seizure-like events. These have been observed to be generally short lived and reversible and the mechanism is yet unknown.

Chimeric antigen receptor clinical trials have expanded rapidly as it is recognised that the technology offers new therapy for conditions that are difficult to treat, having few therapeutic alternatives. However, new clinical trials are being designed to address participants that do not respond to this therapy and the durability of remission of those that do respond.

Research Office

Identification of Scientific Expert Reviewer

- Scientific Expert Reviewers are expected to be independent of the ethics committee. An institution employee may serve concurrently as a member of one or more sub-committees associated with the ethics committee but will recuse themselves if there was a conflict of interest regarding the proposed clinical trial application.
- Institutions are expected to have a list of current Scientific Expert Reviewers including appointment positions, whether honorary, internal or external. Additional details of Scientific Expert Reviewers should align with their Curriculum Vitae, field of expertise, credentials and contact details.
- Institutions should endeavour to establish linkages between HRECs, Medical Research Institutes and Universities to provide a pool of Scientific Expert Reviewers.

Establishing an Institutional Scientific Expert Reviewer Database

- Scientific Expert Reviewer with technical expertise may be associated with either their institution or another organisation.
- Some Scientific Expert Reviewers should have experience in assessing preclinical trial data.

Legal Requirements

To engage a Scientific Expert Reviewer for public health institutions, the following templates are provided in the appendix:

- *Conflict of Interest - Declaration Form*
- *Deed of Acknowledgement of Obligations as an Expert Reviewer*

Professional Indemnity Insurance

External expert reviews should be adequately protected by indemnity provided in respect of liabilities that may arise in the course of review of an early phase clinical trial.

Evidence of professional indemnity insurance should be provided. The Scientific Expert Reviewer will either be:

(i) An employee of a Victorian Managed Insurance Authority (VMIA) insured agency where the Scientific Expert Reviewer is covered under the VMIA Health Program

(ii) Not an employee of a VMIA insured agency.
The Scientific Expert Reviewer should provide the research office with a Certificate of Currency for a professional indemnity insurance policy covering the provision of the service.
If the Scientific Expert Reviewer does not have a current professional indemnity insurance policy or cannot provide information that their professional indemnity insurance policy covers them for the review, the following form must be completed and submitted to VMIA by the responsible health service organisation.

See Appendix III.
Details of Independent Review form and submitted to VMIA via email at contact@vmia.vic.gov.au
When the Scientific Expert Reviewer's insurance coverage is to be considered by the VMIA, certain underwriting information is required. Refer to the template Coverage for Independent Reviewer provided by the VMIA for further information. See Appendix IV.

Governance process

The administrating institution should have a clear policy for engaging a Scientific Expert Reviewer including conflict of interest and confidentiality considerations.

- A scientific expert review data base should be established with Scientific Expert Reviewers that can provide a scientific assessment. Expertise, research discipline, qualifications, credentialing details and the availability of all Scientific Expert Reviewers can be included in the database. The database could include the scientific category and number of research applications commissioned to a Scientific Expert Reviewer for quality assurance purposes (e.g. a sufficient number of reviews undertaken within a specified time period) to ensure the database of Scientific Expert Reviewers maintains its relevance and expertise.
- Review of an early phase clinical trial should be fully documented and triaged to an appropriate Scientific Expert Reviewer according to the required expertise and experience. There should be confirmation of the availability of a Scientific Expert Reviewer before engaging the reviewer.
- Documentation associated with the expert review should clearly state the due date of the review, the date of the ethics committee meeting, and the details of the research office contact person for submitting the documents required to advise the ethics committee.
- The research office has the responsibility for the preparation and provision of materials for the Scientific Expert Reviewer, including review proformas.
- Four specific scientific expert review Proformas and two supplementary review Proformas are designed to assist in assessment of the content of the research application. At a minimum a Scientific Expert Reviewer should use one of the four Proformas, depending on the therapeutic good being used in the clinical trial. Some trials may require multiple Proformas depending on the study product (e.g. combination trial of drug and medical device).

  Proformas for the assessment of a therapeutic good:
  - Toxicology
  - Medicines
  - Medical Devices
  - Biologicals

  Supplementary Review Proformas are focussed on key scientific aspects and should be used, as applicable for the type of clinical trial being reviewed:
  - Biodynamics and Kinetics
  - Immunology

The review proformas form the **Scientific Expert Review Toolkit.** The toolkit should be accompanied by, but not be limited to, the following:

- Investigational Product information including safety data

- Investigator Brochure
- Protocol, including the Risk Management Plan, or the protocol as a separate document
- Participant Information and Consent Form
- Invoice template (if required).

Invoices

The administering institution should have a policy regarding the cost of an expert review service and identify the entity responsible for paying and associated fee for the scientific expert review.

Appendix

Appendix I: Conflict of Interest – Declaration Form

Conflict of Interest - Declaration Form

Surname: .....

Given names: .....

Job or position or role: .....

Name of Institution: .....

Unit: .....

Matter under consideration:

.....

Expected role/duties to be performed by the Expert Reviewer in dealing with this matter:

.....

Private interest identified which have the potential to impact on the employee's ability to carry out, or be seen to carry out, their official duties impartially and in the public interest:

☐ **I do not have a conflict of interest,** to the best of my knowledge, in relation to the matter under consideration.

☐ **The conflict of interest has been identified as an** (double click the check box and then mark 'checked' for the appropriate box)**:**

Actual conflict of interest ☐

(if there is real conflict between an individual's public duties and responsibilities and their private interests or the interests of relatives and friends or even business rivals).

Perceived conflict of interest ☐

(if a third party could form the view that an employee's or contractor's private interests could improperly influence the performance of their duties, now or in the future).

Potential conflict of interest ☐

(if an employee or contractor has private interests that could conflict with their public or official duties).

Pecuniary interest ☐

(if an actual, potential or perceived financial gain or loss may be involved).

Non-pecuniary interest ☐

(non-financial interests such as personal or family relationships, friendships or other relationships that may influence the performance of their official duties).

Details Concerning Conflict of Interest (please attach any relevant documents)

.....

.....

I hereby declare that the above details are correct to the best of my knowledge and I make this conflict of interest declaration in good faith.

.....

Signature (*employee/ Evaluation Panel member*)

Date:

I hereby declare that I have received and appropriately noted this conflict of interest declaration.

.....

Witness Signature (*manager/supervisor/Evaluation Panel Chair*)

Date:

Conflict of Interest – Declaration Form August 2017

Appendix II: Deed of Acknowledgement of Obligations as an Expert Reviewer

Deed of Acknowledgment of Obligations as an Expert Reviewer

By this Deed dated the …….. day of ……. 20.....

I, ……..... [Name of expert reviewer] of

…… [Address of expert reviewer], having agreed to act as an external expert reviewer with specialist expertise in

……[Area/s of Relevant Expertise] (**Expert Reviewer**),

Acknowledge and agree as follows:

1. **Permission to Disclose Personal Details**
   - 1.1 My personal contact details will be made available to a Principal Investigator of the investigational organisation and a nominated member of the participating Human Research Ethics Committee (**HREC**) via a secure and confidential process.
   - 1.2 The above personnel may only contact me in my capacity as an Expert Reviewer, to request that I provide expert assistance in the assessment and review of research proposals.
   - 1.3 Acceptance of a request to assist an HREC in reviewing a particular proposal will be at my discretion alone.

2. **Ethical Obligations.** I certify that, in my capacity as Expert Reviewer, I will comply with the guidelines and legislation detailed in the National Health and Medical Research Council's *National Statement of Ethical Conduct in Research Involving Humans*, as amended from time to time.

3. **Confidentiality Obligations**
   - 3.1 In the course of performing my functions as an expert reviewer, I will be exposed to Confidential Information, as defined below.

   Use of Confidential Information.

   - 3.2 I undertake to:
     - 3.2.1 use the Confidential Information exclusively in connection with requests to provide expert assistance in assessment and review of research proposals for HRECs (**Purpose**), and for no other purpose;
     - 3.2.2 keep all Confidential Information in confidence and only permit officers and employees employed (or otherwise engaged) by me to become aware of the Confidential Information:
       (a) for the purposes of carrying out their duties in connection with the Purpose; and
       (b) who are legally bound under the terms and conditions of their employment agreements (or otherwise) to observe the provisions of this Deed;
     - 3.2.3 not use or disclose, or permit any officers, employees, agents or advisors employed (or otherwise engaged) by me to use or disclose, Confidential Information or any portion of the Confidential Information, except:
       (a) to consultants and professional advisers engaged by me to whom the Confidential Information is disclosed in connection with their involvement with the Purpose, and who owe a duty of confidentiality to me and are aware of my obligations under this Deed; or
       (b) as required by law.

   Security and Control.

   - 3.3 I undertake to:

3.3.1 establish and maintain all necessary security measures to maintain the confidential nature of the Confidential Information, at all times utilising the same degree of care used by me to protect my own confidential and proprietary information of similar importance, in order to safeguard Confidential Information from access or use that is not authorised under this Deed; and

3.3.2 immediately notify the disclosing party of any suspected or actual unauthorised use, copying or disclosure of the Confidential Information.

Return of Confidential Information.

3.4 I undertake to immediately, on request at any time by the disclosing party:

3.4.1 return to the disclosing party;

3.4.2 destroy and certify in writing to the disclosing party the destruction of; or

3.4.3 destroy and permit an employee of the disclosing party to witness the destruction of,

all the disclosing party's Confidential Information, stored in any medium, in my possession or control (including the original medium, copies and that part of notes and other records prepared by me based on or incorporating any Confidential Information).

Right to Disclose But No Other Warranty.

3.5 The disclosing party warrants that it has the right to disclose the Confidential Information. Otherwise, all Confidential Information is provided solely for the Purpose and without any warranty (express, implied or otherwise) regarding the accuracy or completeness of the Confidential Information being given by the disclosing party. The only warranties provided by the disclosing party will be those (if any) contained in a definitive and binding agreement entered into by the parties (if any) in relation to the Purpose.

No Further Rights.

3.6 The Confidential Information remains the property of the disclosing party. The grant of access to the Confidential Information by the disclosing party is not an express or implied licence to use the Confidential Information for any other purpose than the Purpose.

No Obligation.

3.7 The provision of the Confidential Information is not an express or implied representation or warranty that the disclosing party will proceed with the Purpose. The disclosing party may any time advise that it no longer wishes to proceed with the Purpose or no longer wishes to deal with the receiving party in relation to the Purpose.

Interpretation

3.8 **Confidential Information** means:

(a) the existence of the discussions in relation to the Purpose the subject of this Deed;

(b) all unpatented inventions, ideas, know-how, concepts, trade secrets, processes, proprietary technology and techniques and all related information of the disclosing party or any subsidiary and affiliated companies of such party, disclosed or supplied by or on behalf of the disclosing party to the receiving party in connection with the Purpose, whether orally, visually or in documentary or electronic form;

(c) commercial business, technical and proprietary information, pricing information, information regarding products and related documents, manuals, data, research and development plans, product and business plans, strategies, historical and financial results, budgets, forecasts, projections and other financial data, of the disclosing party or any subsidiary and affiliated companies of such party disclosed or supplied by or on behalf of the disclosing party to the receiving party in connection with the Purpose, whether orally, visually or in documentary or electronic form; and

(d) any notes, records or copies made of the information referred to in paragraphs (b) or (c) of this definition,

but excludes information that:

(e) is either in the public domain or comes into the public domain (otherwise than as a result of breach of this Deed by the receiving party or a breach of confidence by any other person); and
(f) the receiving party is compelled to disclose by statute or law provided that the receiving party:
    (i) gives the disclosing party prompt written notice of any impending compelled disclosure;
    (ii) provides reasonable assistance to the disclosing party in opposing the compelled disclosure; and
    (iii) makes only such disclosure as is compelled.

4. **Conflict of Interest.** I declare that for every request for expert review I receive from the investigational organisation, I will disclose all past, current or anticipated interests of entities related to me, or of a significant nature that I have and which may conflict with the performance of, or restrict me in performing my functions as, an independent expert reviewer, in the form set forth in **Schedule A** hereto (**Conflict of Interest – Declaration Form**).

5. **Survival of Provisions.** Any termination of my engagement as Expert Reviewer, whether generally or in respect of any particular research proposal for an HREC, shall not affect the provisions hereof which are intended, by their nature, to survive termination, including but not limited to the confidentiality provisions set forth herein.

6. **Governing Law.** This Deed is governed by the laws of the State of Victoria.

Executed as a Deed Poll by:

....
[Date]

.....
[Name of expert reviewer]

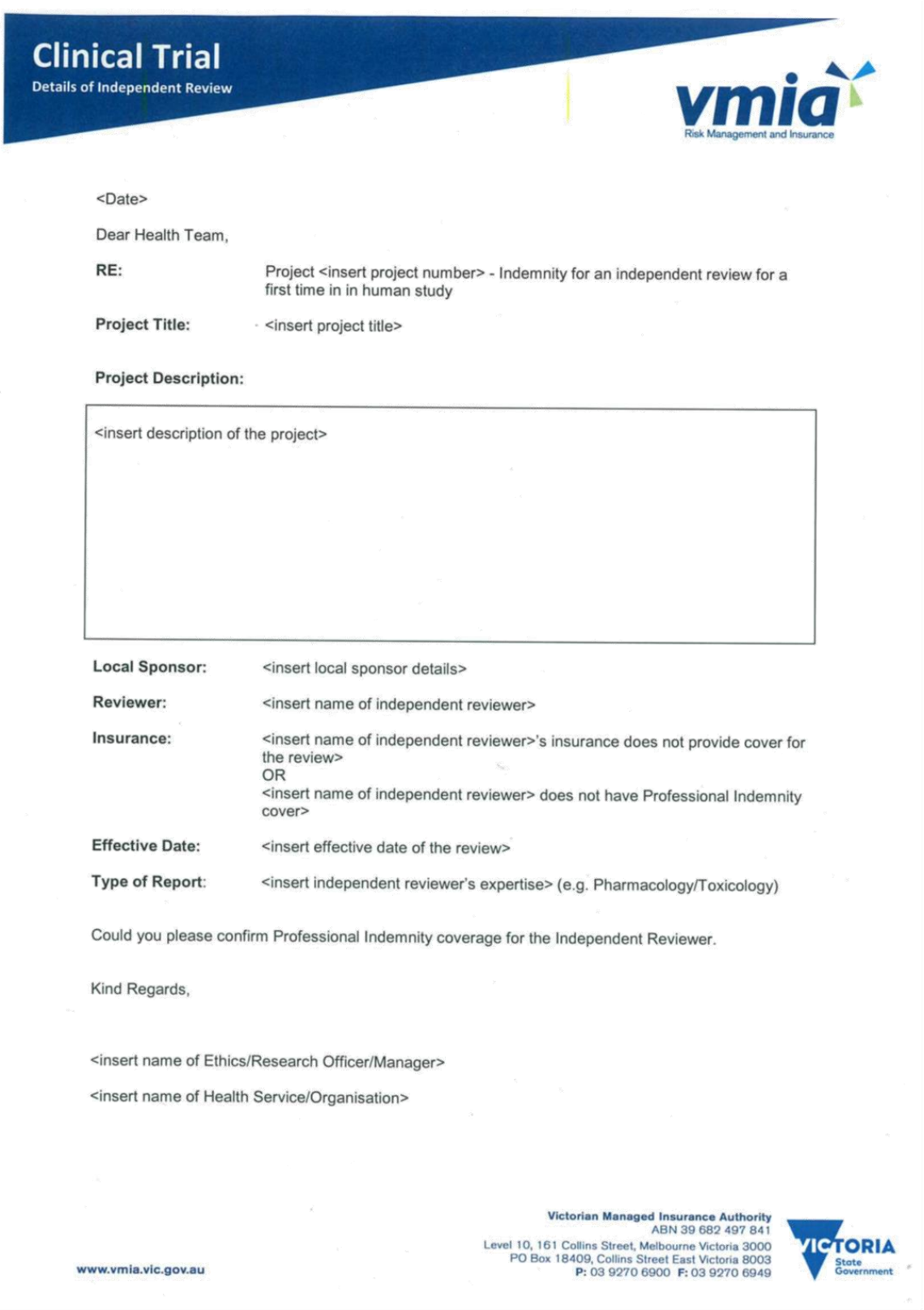
Witnessed by:

....
[Date]

.....
[Name]

Appendix III: Details of Independent Review

A letter to VMIA from the Health Service seeking confirmation of insurance coverage for an expert reviewer. Details of Independent Review



Clinical Trial
Details of Independent Review

vmia
Risk Management and Insurance

<Date>

Dear Health Team,

RE: Project <insert project number> - Indemnity for an independent review for a first time in in human study

Project Title: <insert project title>

Project Description:

<insert description of the project>

Local Sponsor: <insert local sponsor details>

Reviewer: <insert name of independent reviewer>

Insurance: <insert name of independent reviewer>'s insurance does not provide cover for the review>
OR
<insert name of independent reviewer> does not have Professional Indemnity cover>

Effective Date: <insert effective date of the review>

Type of Report: <insert independent reviewer's expertise> (e.g. Pharmacology/Toxicology)

Could you please confirm Professional Indemnity coverage for the Independent Reviewer.

Kind Regards,

<insert name of Ethics/Research Officer/Manager>

<insert name of Health Service/Organisation>

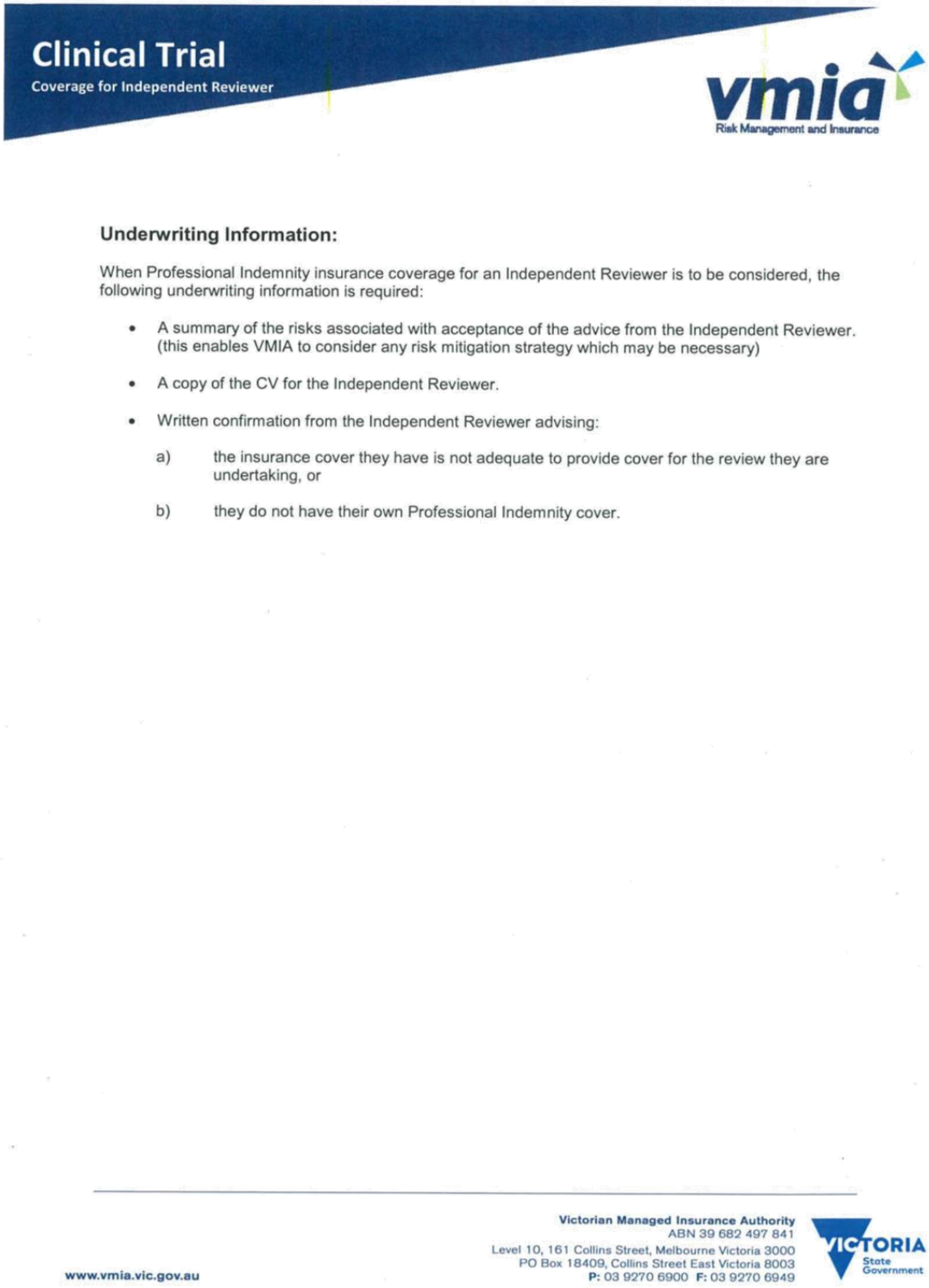
www.vmia.vic.gov.au

Victorian Managed Insurance Authority
ABN 39 682 497 841
Level 10, 161 Collins Street, Melbourne Victoria 3000
PO Box 18409, Collins Street East Victoria 8003
P: 03 9270 6900 F: 03 9270 6949

VICTORIA State Government

Appendix IV: Coverage for Independent Reviewer

Coverage for Independent Reviewer



Clinical Trial

Coverage for Independent Reviewer

vmia Risk Management and Insurance

Underwriting Information:

When Professional Indemnity insurance coverage for an Independent Reviewer is to be considered, the following underwriting information is required:

- A summary of the risks associated with acceptance of the advice from the Independent Reviewer. (this enables VMIA to consider any risk mitigation strategy which may be necessary)
- A copy of the CV for the Independent Reviewer.
- Written confirmation from the Independent Reviewer advising:

  a) the insurance cover they have is not adequate to provide cover for the review they are undertaking, or

  b) they do not have their own Professional Indemnity cover.

www.vmia.vic.gov.au

Victorian Managed Insurance Authority
ABN 39 682 497 841
Level 10, 161 Collins Street, Melbourne Victoria 3000
PO Box 18409, Collins Street East Victoria 8003
P: 03 9270 6900 F: 03 9270 6949

VICTORIA State Government