

INVESTIGATOR RESPONSIBILITIES

Standard Operating Procedure

Western Health

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| SOP reference | 010 |
| Version: | 4.0 dated September 2024 |
| Effective Date | September 2024 |
| Review Date | September 2029 |
| Approved by | Mr Bill Karanatsios, Research Program Director |
| Signature and date | <i>Bill Karanatsios</i> 13/09/2024 |

Amendment History

| VERSION | DATE | AMENDMENT DETAILS |
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| 2.0 | 04 Dec 2015 | |
| 3.0 | June 2019 | Updated to align with MACH SOPs |
| 4.0 | September 2024 | Updated to align with the NHMRC National Statement on Ethical Conduct in Human Research (2023 and updates) and Australian Clinical Trial Handbook – Guidance on conducting clinical trials in Australia using ‘unapproved’ therapeutic goods version 2.4 (October 2021) |

1. AIM

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

2. SCOPE

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

3. APPLICABILITY

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

4. PROCEDURE

For investigator initiated trials where WH is also the sponsor, obligations owed to or emanating from sponsor should be interpreted to mean WH.

1. Investigator Responsibilities

The investigator(s):

| STEP | ACTION |
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| 4.1.1 | Should ensure that clinical studies are carried out according to International Conference on Harmonisation (ICH), regulatory authorities' requirements and any other local requirements. |
| 4.1.2 | Have written evidence of TransCelerate accredited ICH Good Clinical Practice (GCP) training. In order to be considered current and acceptable such GCP training must have been undertaken no more than two years prior to the commencement of a given trial. |
| 4.1.3 | Understand 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. |
| 4.1.4 | Ensure that they are appropriately qualified to conduct the trial. |
| 4.1.5 | Inform the participant's primary physician about the participant's participation in the trial if the participant has a primary physician and if the participant agrees to the primary physician being informed. |

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| 4.1.6 | Note: Although a participant 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 participant's rights. |
| 4.1.7 | Must declare any conflicts of interest, payments etc. from other parties. |
| 4.1.8 | 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. |
| 4.1.9 | Must possess, prior to trial commencement, Human Research Ethics Committee (HREC) approval/endorsement and Research Governance Authorisation of trial protocol, patient information and consent documents, recruitment procedures, consent form updates and any other information given to participants. |
| 4.1.10 | 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 |
| 4.1.11 | Should be able to demonstrate that adequate participant recruitment is likely to be possible, with necessary time available to conduct the study to GCP requirements, and with adequate facilities and trial staff. |
| 4.1.12 | Must present all trial related documents to the HREC for review including the Investigator's Brochure (IB) as well as updates. |
| 4.1.13 | Must document any deviation from the protocol for later review. |
| 4.1.14 | Must ensure that the trial is conducted according to the approved protocol. |
| 4.1.15 | 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 Clinical Trial Notification (CTN) or Clinical Trial Exemption (CTX) trials. |
| 4.1.16 | <p>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.</p> <p>Note: Therapeutic Goods Administration (TGA) CTN notifications are now done electronically through the TGA Business Services (TBS) web portal. A copy should be kept in the Trial Master File (TMF).</p> |
| 4.1.17 | Must ensure accountability of the investigational product at the trial site(s). |
| 4.1.18 | Must ensure that participants have been fully informed and written consent obtained after all trial procedures and risks were adequately explained and that the principles and essential elements of Informed consent are upheld and included in the information document |

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| 4.1.19 | Should be thoroughly familiar with the appropriate use of the investigational product(s), as described in the protocol, in the current IB, in the product information and in other information sources provided by the sponsor. |
| 4.1.20 | Should ensure that all persons assisting with the trial are adequately informed about the protocol, the investigational product(s), and their study-related duties and functions. |
| 4.1.21 | Should submit written summaries of the project status to the HREC and Research Governance Office (RGO) annually, or more frequently, if requested by the HREC or RGO. |
| 4.1.22 | Should provide written reports to the sponsor, the HREC and the institution RGO promptly on any changes significantly affecting the conduct of the trial, and/or increasing the risk to participants. |
| 4.1.23 | Should comply with the applicable regulatory requirement(s) related to the reporting of Suspected Unexpected Serious Adverse Reactions (SUSAR) and Significant Safety Issues (SSIs) to the regulatory authority(ies), Sponsor, HREC and RGO. |
| 4.1.24 | <p>Should promptly inform the researchers participants if the project is prematurely terminated or suspended for any reason as well as the institution and should assure appropriate therapy and follow-up for the participants, and where required by the applicable regulatory requirement(s), inform the regulatory authority(ies).</p> <p>Note: if the investigator terminates or suspends a project 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.</p> |
| 4.1.25 | Should, upon completion of the project, where applicable, inform the institution RGO; 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.

Associate Investigator (AI)

Any individual member of the clinical trial team designated and supervised by the investigator at a study site to perform critical study-related procedures and/or to make

important study-related decisions (e.g., associates, residents, research fellows). Also referred to as “Sub-Investigator”.

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 participants are protected.

Human Research Ethics Committee (HREC)

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

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

Informed Consent

A process by which a participant 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 participant's decision to participate. Informed consent is documented by means of a written, signed and dated informed consent form.

Institution

An institution named as a Participating Site on an Ethical Approval issued by the reviewing 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's Brochure (IB)

The document containing a summary of the clinical and non-clinical data relating to an investigational medicinal product or device that are relevant to the study of the product or device in humans.

Principal Investigator (PI)

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.

Research Governance Office (RGO)

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

Significant Safety Issue (SSI)

A safety issue that could adversely affect the safety of participants or materially impact on the continues ethical acceptability or conduct of the trial.

Sponsor

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

Suspected Unexpected Serious Adverse Reaction (SUSAR)

An adverse reaction that is both serious and unexpected

Therapeutic Goods Administration (TGA)

Australia's regulatory agency for medical drugs and devices.

Trial Master File (TMF)

A file that contains all the applicable essential documents that demonstrate that the study/trial has been conducted in accordance with regulatory requirements and ICH GCP, enabling both the conduct of a project and the quality of the data produced to be evaluated. The preparation and maintenance of the Study File resides with the Site Investigator and set up at the start of a trial and is archived at the end of the trial. This may also be called the "Study Site Master File" or "Investigator Site File".

6. REFERENCES

1. Based on VMIA GCP SOP No.010 Version:1.0 Dated 17 September 2007
2. Based on MACH GCP SOP No.010 Version 1.0
3. Note for guidance on Good Clinical Practice (CPMP/ICH/135/96) annotated with TGA comments DSEB, July 2000, sections 4.
4. Therapeutic Goods Act 1989
5. Standard Operating Procedures for Clinical Investigators, World Health Organisation, version 1.1.
6. Australian Clinical Trial Handbook – Guidance on conducting clinical trials in Australia using 'unapproved' therapeutic goods version 2.4 (August 2021)
7. NHMRC Safety Monitoring and Reporting in Clinical Trials Involving Therapeutic Goods (2016)
8. NHMRC National Statement on Ethical Conduct in Human Research (2023 and updates)

7. AUTHORS/CONTRIBUTORS

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8. PRIMARY PERSON/DEPARTMENT RESPONSBLE FOR DOCUMENT

Western Health Office for Research






WH GCP SOP 010 Investigator Responsibilities v4 Sept24_FINAL

Final Audit Report

2024-09-13

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| Created: | 2024-09-13 |
| By: | Kaiyan Mak (kaiyan.mak@wh.org.au) |
| Status: | Signed |
| Transaction ID: | CBJCHBCAABAAzsKMthIP0S17C0e2PeyB7hFEQeJk3_yr |

"WH GCP SOP 010 Investigator Responsibilities v4 Sept24_FINAL" History

-  Document created by Kaiyan Mak (kaiyan.mak@wh.org.au)
2024-09-13 - 3:10:12 AM GMT
-  Document emailed to Bill Karanatsios (bill.karanatsios@wh.org.au) for signature
2024-09-13 - 3:10:16 AM GMT
-  Email viewed by Bill Karanatsios (bill.karanatsios@wh.org.au)
2024-09-13 - 4:25:49 AM GMT
-  Document e-signed by Bill Karanatsios (bill.karanatsios@wh.org.au)
Signature Date: 2024-09-13 - 4:25:57 AM GMT - Time Source: server
-  Agreement completed.
2024-09-13 - 4:25:57 AM GMT