# CLINICAL TRIALS ADVERSE EVENTS MANAGEMENT STANDARD OPERATING PROCEDURE (SOP)

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## 1. Introduction

### 1.1 Overview

One of the main objectives of any clinical trial is to assess the efficacy and safety of an intervention compared to a control or other intervention. All trials therefore expose participants to risk, although in many cases, the risks may be no greater than what they may experience in routine clinical practice.

The existence and nature of adverse events has major impact on deciding whether an intervention is safe for use. In order to minimize risk and rapidly detect unexpected harm all adverse events should be monitored, assessed, and recorded as well as reported to ensure that the rights, safety and welfare of clinical trial participants is protected

### 1.2 Purpose

This standard operating procedure (SOP) describes how to manage adverse events during a clinical trial. It outlines the importance of monitoring, assessing, recording and reporting adverse events all of which are a critical part of research site activities during a clinical trial.

### 1.3 Scope

The Principal Investigator (PI) at the clinical trial site has overall responsibility for adverse event monitoring, assessment, recording and reporting. PI can delegate some aspects of this process to Sub- investigators and/or clinical research nurses/study coordinator

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## 2. Terminology – Abbreviations and Definitions

Based on the International Conference of Harmonization (ICH) Guidelines (ICH E6 R2 and ICH E2A). Listed below are some of the most internationally accepted and common abbreviations along with definitions/terms of reference used in clinical trials

| | | |
|---|---|---|
| **PV** | **Pharmacovigilance** | Defined as the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug-related problem with the aim to enhance patient care and safety in relation to the use of medicines. |
| **DSUR** | **Development Safety Update Report** | Annual safety report submitted to Research Ethics Committee, and other parties as applicable. The report is a comprehensive, scientific review and evaluation of pertinent safety information collected during the reporting period related to a drug under investigation whether marketed or not. |
| **PSURs** | **Periodic Safety Update Reports** | These are periodic evaluation reports of risk-benefit balance of a medicinal product. These provide an analysis of its safety and efficacy profiles throughout its life cycle. |
| **AE** | **Adverse Event** | Any untoward medical occurrence experienced by the clinical trial participant, with unfavorable or unintended signs, symptoms or disease temporally associated with an administered pharmaceutical product (or active control/placebo) which does not necessarily have a causal relationship with the product. |
| **SAE** | **Serious Adverse Event** | Any untoward medical occurrence that:<br>a) results in death<br>b) Is life-threatening<br>c) Requires inpatient hospitalization or prolongation of existing hospitalisation<br>d) Results in persistent or significant disability/incapacity, or<br>e) Is a congenital anomaly/birth defect |
| **SUSAR** | **Suspected Unexpected Serious Adverse Reaction** | An adverse event which is serious and suspected of being related to the investigational product (causality) or unexpected (not listed in the investigator's brochure) |
| **IME** | **Important Medical Event** | An event that may not be immediately life threatening or result in death or hospitalization but may jeopardise the health of the clinical trial participant or may require intervention to prevent serious harm. |
| **AESI** | **Adverse Event of Special Interest** | An event that can be serious or non-serious that is of scientific and medical concern specific to the sponsor's product or program, for which ongoing monitoring and rapid communication by the investigator to the sponsor is required |
| **ADR**<br>**SADR** | **Adverse Drug Reaction (ADR) or Serious Adverse Drug Reaction (SADR** | An adverse event in which there is reasonable possibility (possibly or probable) of a causal relationship between the investigational product and event**. (Implication of causality)** |

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|---|---|---|
| **IMP** | **Investigational Medical 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 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 |
| **IMD** | **Investigational Medical Devices** | A medical device that has not received regulatory approval for marketing and is being investigated in a clinical trial to evaluate the efficacy and safety of the device |
| | **Biological** | An item made from, or containing, human cells or human tissues, that is used:<br>• To treat or prevent disease/injury<br>• Diagnose a condition of a person<br>• Alter the physiological processes of a person<br>• Test the susceptibility of a person to disease,<br>• Replace or modify a person's body part(s) |
| **MedDRA** | **Medical Dictionary for Regulatory Activities** | Standardized international medical terminology dictionary that can be used for regulatory communication and evaluation of data pertaining to medicinal products for human use |
| **CSR** | **Clinical Study Report** | The final document containing information on conduct, results and interpretation of the trial |

## 3. Pharmacovigilance Reporting

The World Health Organization (WHO) defines pharmacovigilance (PV) as "the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug-related problem."

The reporting of suspected adverse events or adverse reactions to medicines is fundamental to pharmacovigilance. New Zealand Pharmacovigilance Agencies are:

- **MEDSAFE (Medicines and Medical Devices Safety** ) Authority - Pharmacovigilance Agency for Clinical Trials
- **CARM (Centre for Adverse Reactions Monitoring)** - Agency for processes all reports of registered and unregistered adverse reactions and maintaining a database of all these events.
- **MARC (Medicines Adverse Reactions Committee)** - Ministerial advisory committee of general practitioners and medical specialists overseeing spontaneous adverse reaction reporting scheme

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## 4. Key Research Roles and Responsibilities

| Role | Responsibility |
|---|---|
| **Study Sponsor**<br>An individual, company, institution, organization that takes responsibility for the initiation, management, and/or financing of the research | In accordance with ICH-GCP, the Sponsor has overall responsibility for the ongoing safety monitoring for duration of the clinical trial and post-approval for the life cycle of the medicinal product. |
| **Medical Monitor (MM)**<br>Medically qualified individuals providing 24hr emergency coverage on all safety-related matters. | To ensure safety and integrity of the trial from the initial design of the study to the final closeout. Medical monitors act as point of reference for study team members and investigative sites, determining how to evaluate safety events within a clinical trial |
| **Clinical Research Organization (CRO)**<br>Contract Research organization an entity that assumes one or more of the obligations of a Sponsor, as an independent contractor to the Sponsor | Plan, coordinate, execute, and supervise the processes involved in the development of a clinical trial, being a central contact point between the sponsor and other trial parties (e.g. ethics committees, regulatory agencies, vendors, and hospitals. |
| **Clinical Research Associate (CRA)**<br>Also known as monitor is an individual employed by either a pharmaceutical company or a Contract research organization | Responsible for coordinating and overseeing the execution of studies and clinical trials at site level. Usually involved in every aspect of the clinical trial |
| **HDECs**<br>The Health and Disability Ethics Committee is a Central ministerial committee set up to oversee the review of clinical studies for many different organizations | **To secure the benefits of health and disability research by checking that all research meets or exceeds established ethical standards**<br>• Responsible for ensuring the protection of the rights, safety and well-being of human subjects involved in a clinical trials. By discussing the clinical trial's scientific, ethical, and legal ramifications they evaluate the benefit/risk factors of the clinical trial<br>• Responsible for monitoring and reviewing any medical research involving human subjects.<br>• This team has the authority to approve or disapprove research and ask for research modifications prior approval<br>• Responsible for reviewing, approving, and providing continuing review of trial protocol and amendments and of the methods and material to be used in obtaining and documenting informed consent of the trial subjects |
| **HREC**<br>Human Research Ethics Committee reviews research proposals from all Faculties and research units within a University | |
| **Institutional or Independent Review Board (IRB) or Independent or Institutional Ethics Committee (IEC)**<br>Committee or Board comprised of medical, scientific, and non-scientific members, support individual research institutions with the responsibility of reviewing clinical trials | |
| **National Ethics Advisory Committee - NEAC**<br>Independent advisor to the Minister of Health which **Sets Ethical standards for research** | Provides advice to the Minister on a range of issues, including on the system of ethical review of research and on the conduct of clinical trials in New Zealand, and ethical issues in elective health care services. |

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|---|---|
| **Clinical Event Committee - CEC**<br>An independent committee of medical experts. | Review specific information obtained from research participants. Primary role is to provide independent expert review of data on clinical events based on protocol-specific definitions during a clinical trial |
| **Data and Safety Monitoring Board - DSMB**<br>**Data and Safety Monitoring Committee -DSMC**<br>An impartial group of individuals | To oversee a clinical trial and review the results to see if they are acceptable. This group determines if the trial should be changed or closed. |
| **Coordinating Investigator or National Lead**<br>An investigator assigned responsibility for the coordination of investigators at different centers participating in a multicenter clinical trial | Responsible for submitting the trial for scientific and ethical review and any ongoing communication with the reviewing HREC or their institutional research governance office |
| **Principal Investigator - PI**<br>Person responsible for the conduct of the clinical trial at a site. If a trial is conducted by a team of individuals at a trial site, the investigator is the responsible leader of the team | Responsibility to ensure participant are:<br>• Informed of the risks and benefits of participating in the study as well as the compensation provisions for research related injury during the informed consent process.<br>• Given contact details of the study team as needed including 24/7 emergency phone number<br>• Educated about adverse events/reactions, and the importance of reporting them to the site staff at study visits and/or during telephone contact.<br>• Reporting SAE to Sponsor/CRO, Ethics committee and all members of site study staff<br>• Evaluating adverse events for seriousness, causality, severity, and if stated in the protocol, expectedness of each event<br>• Responsible for the accuracy, completeness and timeliness of records and reports. |
| **Research Team**<br>Team of people involved in running a clinical trials<br>A study team may consists of:<br>• Sub-Investigator or co-investigator<br>• Study Coordinator<br>• Research Nurse<br>• Pharmacist<br>• Laboratory personnel<br>• Research officer/Research fellow<br>• Research assistant | Each member will have designated roles and responsibilities through delegation by the PI who maintains overall responsibility for conduct of the clinical trial.<br>Members in contact with clinical trial participants should monitor for adverse events.<br>They are responsible for documenting and reporting adverse events working closely with the PI |
| **Clinical Trial or Research Participant**<br>Individual participating in research sometimes referred to as human subjects or study volunteers. | • To take the trial medication according to study guidelines<br>• Report of any observation/untoward event, possible side-effect during the trial<br>• Report any changes in concomitant medication use or medical history/ongoing medical care |

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## 5. Adverse Event Reporting Procedure

The adverse event-monitoring phase starts **immediately after signing of consent** and continues throughout the study up to a protocol-defined end-point.

Following signing of informed consent and before any trial intervention, PI should complete a **baseline assessment** including any baseline diagnostic procedure if required by the study protocol (e.g. radiological, laboratory assessments) in order to:

- Understand the participant's past medical history and
- Current health status (including any symptoms present at baseline)

### 5.1 Identification of Adverse Events

At each contact with the trial participant, the investigator must seek information on adverse events by

a) **Specific questioning**
Participants self-reporting is important and use non-leading questions to assess for AEs, e.g. "Have you been feeling any different since your last visit?" instead of "Have you been sleeping well?"

b) **Completing assessments** including physical examination (including skin assessment), safety bloods, ECG or any radiological imaging as required by study protocol

c) **Monitoring for changes** to concomitant medications.
The reason for change to understand whether there is a causal relationship with the investigational product or worsening of an existing medical condition
The worsening (in frequency or severity) of an existing condition also constitutes an adverse event I.e. Gout flare-up, acute on chronic renal failure etc.

d) **Receiving an Alert from** inpatient management system (iPM). All participants in research projects require close monitoring during participation in a clinical trial to assure their safety at all times. As part of the safety monitoring process the study coordinator or Investigator, add a National Medical Warning (NMW) and/or medical alert via Patient Information Management System (iPM) once a participant enrols into the interventional Clinical trial and/or medical device trials.

### 5.2 Evaluation

PI or delegated staff should evaluate the adverse event for

1. **Seriousness**
Event considered "serious" if, in the view of either the investigator or sponsor, results in any of the following outcomes: Death. A life-threatening adverse event. Inpatient hospitalization, or prolonged of existing hospitalization.

2. **Causality**
The PI or delegated staff should use clinical judgement to determine the relationship by considering all possibilities. i.e. Alternative causes, such as natural history of the underlying diseases or Concomitant therapy to categorize the event for reporting as

- **Not Related**: Temporal relationship of the onset of the event, relative to administration of the product, is not reasonable or another cause can explain the occurrence of the event.
- **Unlikely:** Temporal relationship of the onset of the event, relative to administration of the product, is likely to have another cause for occurrence of the event.

- **Possibly related**: Temporal relationship of the onset of the event, relative to administration of the product, is reasonable but the event could have been due to another, equally likely cause.
- **Probably related**: Temporal relationship of the onset of the event, relative to the administration of the product, is reasonable and likely explained by the product than any other cause.
- **Definitely related**: temporal relationship of the onset, relative to administration of the product, is reasonable and there is no other cause to explain the event, or a re-challenge (if feasible) is positive

3. **Severity – (Grading of Event)**

   There is often a lot of confusion about the difference between a severe adverse event and a serious adverse event.

   The PI or delegated staff member need to categorize the severity of the event as:

   - **MILD**: An event easily tolerated by the patient, 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 that prevents normal everyday activities.

4. **Expectedness**

   Determine whether the event as defined in the study protocol is expected or unexpected reactions not previously described in the protocol

   The safety section of each study protocol usually defines:

   - Which AEs are expected and therefore do not need to be recorded in the CRF AE log unless they are required as part of the primary or secondary outcomes.
   - Which SAEs are expected and therefore not reported on an SAE form within 24 hours to the Sponsor (or delegate). These SAEs will still need recording on the CRF AE log.
   - Which SAEs are to be recorded and reported within 24 hours

## 5.3 Documentation and Reporting

Following identification and evaluation of an event record all-pertinent information about the event into participant's source documents, medical record and the sponsor nominated electronic case report form (eCRF).

**Key Elements required for Adverse Event Reporting:**

- Onset date of AE
- Term or description for the AE (where possible use a single term for diagnosis instead of reporting multiple symptoms)
- Record clinically significant lab test values that are different from baseline as AEs unless expected according to the protocol or normal for the patient's condition.
- Severity/grade of the AE (e.g., mild, moderate, severe)
- Relatedness of AE to intervention (e.g., not related, unlikely, possibly, likely, definitely related)
- Serious AE status (yes, no)
- Action taken/treatment provided due to AE
- Outcome of event (e.g., resolved, resolved with sequalae, not resolved, fatal, unknown)
- Date the AE resolved
- Initials/signature of assessor and date of review and assessment

### 5.4 Follow-up

Assess all adverse events for trends in nature and frequency on an ongoing basis throughout the trial.
Record any follow-up information of the event in the patient's medical records
The clinical course of each event should be followed until resolution, stabilization, or until it has been determined that the study treatment or participation is not the cause

## 6. Serious Adverse Event Reporting Procedure

As soon as possible and within 24 hours of becoming aware of a serious adverse event, complete the initial SAE paper or electronic report form. Initial SAE report form must have an assessment of severity, seriousness and causality completed by PI or delegated staff

- Email scanned copy of the paper SAE form to the nominated sponsor safety reporting email address
- File the original signed SAE form in the safety section of the Investigator Site File.
- All events that are still ongoing at the end of the study period must be followed-up to determine the outcome.
- Report immediately to Sponsor and Medsafe any serious adverse event that occur after completion of study period and considered possibly related to the study treatment or study participation

### 6.1 Sponsor reporting requirements to MEDSAFE

**Report within 7 days** all serious adverse events considered suspected, or unexpected or serious adverse reactions (SUSAR) or fatal/Life- threatening **occurring within New Zealand** if they meet the following criteria:

- Are unexpected because they are not outlined in the investigators brochure
- Are not defined study end-points e.g. death or hospitalisation
- Occur in patients located in *New Zealand*; **and**
- Result in a decision to break the study code

**Report within 7 days** any overseas study using the investigational product that stop due to serious or unexpected adverse events. Stating clearly the reasons for halting the study as well as outlining the provisions made for halting the study in New Zealand in the report.

All other SAEs including Serious Unexpected adverse reactions (SUSARs) reported **within 15 calendar days.**

PSURs (Periodic Safety Update Reports): are required only upon request by Medsafe or if a product(s) is included in a submission to Medsafe on a safety issue(s)

### 6.2 Other Sponsor Reporting Requirements

The sponsor is also required to submit routine progress reports to Medsafe at 6monthly intervals.
The reports submitted must describe:

- How the study is progressing
- The number of participants included in relation to the number expected
- The number of dropouts and withdrawals
- If the planned time schedule is still appropriate

New data on the investigational product, detailing the possible impact on the conduct and ethical consideration of the study An analysis of the unblinded serious adverse event reports for the investigational product(s) with respect to possible causality and impact on the continuation of the study

## 6.3 Clinical Trial Site Reporting Requirements

Safety reporting guidelines ICH E6 R2 and ICH E2A section 4.11 recommend:

**To Sponsor**

All SAEs be reported immediately with the exception of those not needing immediate reporting as defined in study protocol or other document e.g., Investigator's Brochure (IB).

**Key Elements required for initial SERIOUS ADVERSE EVENTS report submission:**

- Onset date of AE
- Subject number
- Date of birth
- Subject demographics
- Date of the report
- Description of event, including relationship to study drug
- Determination of seriousness
- Possible cause of SAE other than trial medication
- Relevant medical conditions
- Concomitant medications
- Principal Investigator's name
- Name and telephone number of person reporting the event

- Adverse events and/or laboratory abnormalities identified in the protocol as critical to safety evaluations reported in accordance to the reporting requirements as stated within the time-periods specified in the protocol.
- For reported deaths, the investigator should supply the sponsor and the IRB/IEC with any additional requested information (e.g., autopsy reports and terminal medical reports)
- Investigator should also comply with any applicable country regulatory requirement(s) for related to the reporting of unexpected serious adverse drug.

New Zealand Ethics Committee (HDEC) does not require reporting of site individual AE's and SAEs. For detailed information about NEW ZEALAND HDEC requirement for Visit http://ethics.health.govt.nz/operating-procedures

**To other Health Professionals**

Inform other clinicians involved in the participant's care, including all research team members as well as participant's GP about any safety issues and serious adverse events.

**To the participant**

- Explain that adverse event monitoring is a routine part of the study and why it is necessary
- Reassure participant that will be closely monitored and that adequate measures will be taken
- Reassure the participant that while all events will be recorded, they will be carefully assessed for clinical significance and relatedness to the intervention
- Record event in the participant's paper/electronic clinical records and/or using the "Clinical Trial Visit" template in Concerto

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## 7. Pregnancy Reporting

Although pregnancy is not classified as SAE when occurring in clinical trials of investigational products it is however an important event that requires regulatory reporting and follow-up.
Follow-up of pregnant participant or partner of a male participant until termination or to term of pregnancy to ensure absence of congenital anomaly or birth defect that may have resulted from maternal exposure or transmission of the study drug via semen following paternal exposure.

During screening women of childbearing prior to entering the study agree to avoid pregnancy and male participants agree not to impregnate partners due to the potential risks due to transfer of an investigational product via semen is unknown in most cases. Despite this, even when precautions are taken pregnancy may occur during research participation. Investigators must be aware of the requirements related to reporting and follow-up in the event a research participant or a research participant's partner becomes pregnant.

**Sponsor must:**
Provide an adequate plan in study protocol for managing unexpected pregnancies during the clinical trial specifying:

- What data points will be sought from pregnant research participants or pregnant partners
- Identify if follow-up information will be self-reported or acquired via chart review
- The frequency and length of follow-up required
- Reporting procedure of a pregnancy, an abnormal outcome for the fetus/child, or adverse reactions suspected in infants following exposure to breast milk to the appropriate entities (IRB, sponsor, FDA, etc.) as applicable.
- The protocol should describe the process for monitoring and managing special circumstances in regard to partner privacy for monitoring pregnancy of partner of male trial participant as privacy follow-up may become an issue in certain i.e. cases where the pregnant partner is a minor, where the partner does not wish to be identified, (where paternity question, etc.).
- Provide approved consent forms

**Site must**

- Report the sponsor as soon as possible any pregnancy occurring during the clinical trial whether it is the trial participant or partner to
- Obtain consent of all parties involved prior to collecting any information
- Collect all the required information as specified in the study protocol
- Follow-up the pregnancy for time period specified in protocol
- Notify ethics committee or lead site

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## 8. Coding of Adverse Events for Pharmacovigilance

Coding of AEs is an essential part of pharmacovigilance and vital for signal detection (e.g. of unsuspected harmful effects) as well as safety analysis.

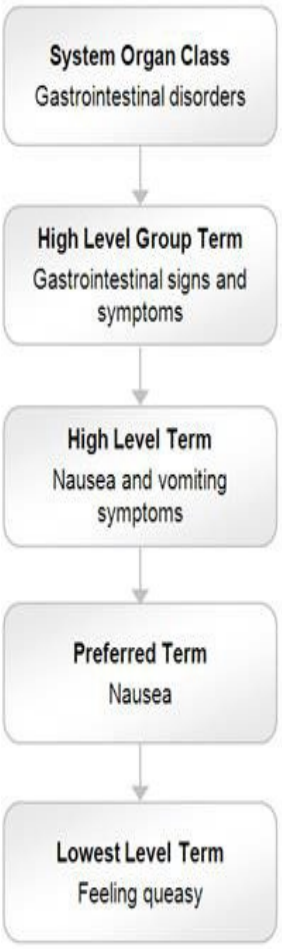
MedDRA is Medical Dictionary for Regulatory Activities with international standardisation of medical terminology used by pharmaceutical and medical device industry as well as regulatory agencies throughout the drug development process in clinical trials. It used for post-marketing activities such as pharmacovigilance (periodic safety update reports and adverse drug reactions), clinical reports, data presentation and coding.

It provides a classification system for diseases, diagnoses, signs, symptoms, therapeutic indications, investigations and procedures, and medical/social/family history.

The dictionary uses a hierarchy system to categorize medical terminology.

The five levels of the dictionary are

1. System Organ Class (SOC),
2. High Level Group Term (HLGT),
3. High Level Term (HLT),
4. Preferred Term (PT)
5. Lowest Level Term (LLT)




**Example**

Coding for term **"queasy"** would be the preferred equivalent medical term (PT) is **"Nausea"** in the context of the following hierarchy:

1. System Organ Class (SOC) = Gastrointestinal disorders
2. High Level Group Term (HLGT) = Gastrointestinal signs and symptoms
3. High Level Term (HLT) = Nausea and vomiting symptoms
4. **Preferred Term (PT) = Nausea**
5. Lowest Level Term (LLT) = Feeling queasy

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## 9. References

Adams-Phipps, Jupiter; Toomey, Danny; Więcek, Witold; et al. (11 October 2022). "A Systematic Review of Human Challenge Trials, Designs, and Safety". Clinical Infectious Diseases. https://academic.oup.com/cid/advance-article/doi/10.1093/cid/ciac820/6758436?login=fals

CARM - New Zealand Pharmacovigilance Centre: https://nzphvc.otago.ac.nz/carm/

EMEA Guideline on the exposure to medicinal products during pregnancy: Need to post-authorisation data, November 2015
https://www.ema.europa.eu/en/documents/regulatory-procedural-guideline/guideline-exposure-medicinal-products-during-pregnancy-need-post-authorisation-data_en.pdf

Guidance on Collecting Data on Pregnancy and Outcomes of Pregnancy from VA Research Subjects and Pregnant Partners of VA Research Subjects for Safety Monitoring
https://www.research.va.gov/resources/policies/guidance/pregnancy.pdf

Guideline on the Regulation of Therapeutic Products in New Zealand: Part 8
**https://www.medsafe.govt.nz/regulatory/guideline/grtpnz/part-8-pharmacovigilance.pdf**

Guideline on the Regulation of Therapeutic Products in New Zealand: Part 11
**https://medsafe.govt.nz/regulatory/Guideline/GRTPNZ/Part11.pdf**

ICH Guidelines
**https://www.ich.org/page/ich-guidelines**

MedDRA Hierarchy
https://www.meddra.org/how-to-use/basics/hierarchy

MedSafe: Your Guide to Adverse Reaction Reporting
https://www.medsafe.govt.nz/profs/puarticles/adrreport.htm

National Ethical Standards for Health and Disability Research and Quality Improvement
http://neac.health.govt.nz/streamlined-ethical-guidelines-health-and-disability-research

National Ethics Advisory Committee. 2019. National Ethical Standards
for Health and Disability Research and Quality Improvement. Wellington: Ministry of Health
https://neac.health.govt.nz/

NHMRC Guidance - Safety monitoring and reporting in clinical trials involving therapeutic goods, November 2016
https://www.nhmrc.gov.au/sites/default/files/images/NHMRC-guidance-safety-monitoring-and-reporting.pdf

Standard operating procedures for Health and Disability Ethics Committees. Version 3.0 dated December 2019. New Zealand Health and Disability Ethics Committees' website: http://www.ethics.health.govt.nz

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## 10. Appendix

### ADVERSE EVENT FLOWSHEET (EXAMPLE)

Please record all Adverse Events that occur during the study and spontaneously reported for 30 days after end of treatment below. Please ensure the investigator provides the assessments for severity and relationship to study medication. The investigator must initial in the space provided beside each entry.

| **Adverse Event** | **Start Date** | **Stop Date** | **Out-come** 1=Resolved; 2=Resolved with sequelae; 3=Continuing 4=Fatal | **Treatment Required** 0=None; 1=Concomitant Medications; 2=Non-Drug Therapies; 3=Concomitant Medications and Non-Drug Therapies | Severity grading 1 = Mild 2=Moderate 3= severe | **Relationship to Study Drug** 1=Not Related 3=Possible; 4= Probable; 5=Definite | **Action Taken with Study Drug** 0=None 1=Study drug interrupted 2=Study drug discontinued | **Was Event Serious*** (definition below) | **Assessed by: PI Initials and Date** |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | ☐ **Yes** ☐ **No** | |
| | | | | | | | | ☐ **Yes** ☐ **No** | |
| | | | | | | | | ☐ **Yes** ☐ **No** | |
| | | | | | | | | ☐ **Yes** ☐ **No** | |
| | | | | | | | | ☐ **Yes** ☐ **No** | |
| | | | | | | | | ☐ **Yes** ☐ **No** | |
| | | | | | | | | ☐ **Yes** ☐ **No** | |
| | | | | | | | | ☐ **Yes** ☐ **No** | |

*SAE definition: Any event that results in any of the following outcomes: death, life threatening, requires inpatient hospitalization or prolongs existing hospitalization, persistent or significant disability and/or incapacity, congenital anomaly/birth defect; important medical events.
Report all SAEs to the sponsor within 24 hours of becoming aware of the event