MEDSAFE
New Zealand Medicines and Medical Devices Safety Authority

New Zealand Association of Clinical Research

Guideline on the Regulation of Therapeutic Products in New Zealand

Clinical trial safety monitoring and reporting for investigational products (medicines and medical devices)

Edition: 1.0

Draft for consultation – August 2024

MANATŪ HAUORA

Contents

Definitions

Adverse Drug Reaction (ADR)	In the pre-approval clinical experience with a new medicinal product or its new usages, particularly as the therapeutic dose(s) may not be established: All noxious and unintended responses to a medicinal product related to any dose should be considered adverse drug reactions.
Adverse Event (AE)	Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An adverse event (AE) can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product
Adverse Events of Special Interest (AESI)	An event (serious or non-serious) of scientific and medical concern specific to the sponsor's product or programme, for which ongoing monitoring and rapid communication by the investigator to the sponsor can be appropriate. Such an event might warrant further investigation in order to characterise and understand it. Depending on the nature of the event, rapid communication by the trial sponsor to other parties (e.g., regulators) might also be warranted
Approved medicine	A medicine which has been granted consent under section 20 (full consent) or section 23 (provisional consent) of the Medicines Act to be sold, supplied, distributed or advertised in New Zealand (sometimes referred to as having **marketing authorisation** or **consent to distribute**).
Approved conditions (of an approved medicine)	Approved conditions of a medicine are the particulars generally outlined in the sponsor's data sheet and displayed in the Medsafe product application search. These include but are not limited to indications, contraindications, dose, administration and manufacturing.
Clinical trial monitor (or clinical research associate)	The clinical trial monitor (or clinical research associate) oversees the progress of a clinical trial, and of ensures that it is conducted, recorded, and reported in accordance with the protocol, Standard Operating Procedures (SOPs), Good Clinical Practice (GCP), and the applicable regulatory requirements.
Data Safety Monitoring Committee (DSMC)	An independent data monitoring committee that may be established by the sponsor to assess at intervals the progress of a clinical trial, the safety data, and the critical efficacy endpoints, and to recommend to the sponsor whether to continue, modify, or stop a trial. Also known as **Data Safety Monitoring Board (DSMB)**.
Development Safety Update Report (DSUR)	The Development Safety Update Report is an annual review of safety information during clinical trials of a medicine under

	investigation – whether or not it is marketed. The main objectives of a Development Safety Update Report is to: Summarise the current understanding and management of identified and potential risks.
Device deficiencies	Any inadequacy in the identity, quality, durability, reliability, safety or performance of an investigational device, including malfunction, use errors.
Gene Technology Advisory Committee (GTAC)	A Committee of the HRC that undertakes scientific assessment of clinical trials that involve the introduction of nucleic acids, genetically manipulated micro-organisms, or viruses or cells into human subjects. It also makes recommendations to the Director-General of Health on whether or not trials should be approved.
Health and Disability Ethics Committee (HDEC)	The Health and Disability Ethics Committees (HDECs) are Ministerial committees (established under section 87 of the Pae Ora (Healthy Futures) Act 2022), whose function is to secure the benefits of health and disability research by checking that it meets or exceeds established ethical standards.
Health Research Council (HRC)	The Health Research Council is responsible for • advising the Minister of Health on national health research policy • Advising on health research priorities for New Zealand • Initiating and supporting health research • Fostering the recruitment, training and retention of health researchers in New Zealand.
Important identified risk; important potential risk	An identified risk or potential risk that could have an impact on the risk-benefit balance of the product or have implications for public health.
Individual Case Safety Report (ICSR)	The complete information provided by a reporter at a certain point in time to describe an event or incident of interest. The report can include information about a case involving one subject or a group of subjects.
Institution (medical)	Any public or private entity or agency or medical or dental facility where clinical trials are conducted.
Investigator	The investigator is responsible for overall conduct of the study at the clinical site, including directing the administration or dispensing of the investigational product to the subject and ensuring that data are collected and maintained in accordance with the protocol and applicable regulatory requirements.
Investigator Brochure (IB)	The Investigator's Brochure (IB) is a compilation of the clinical and nonclinical data on the investigational product(s) that are relevant to the study of the product(s)
Investigational Medicine/ Investigational Medicinal Product (IMP)	A pharmaceutical form of an active ingredient or placebo being tested or used as a reference in a clinical trial, including an approved medicine when used or assembled (formulated or packaged) in a way different from the approved form, when otherwise used outside of its approved conditions (eg, an unapproved indication), or when used to gain further information about an approved use.

Investigational Medical device (IMD)	A medical device being assessed for safety or performance in a clinical investigation.
Medical device	Any instrument, apparatus, implement, machine, appliance, implant, software, material or other similar or related article: a. intended, by the person under whose name it is or is to be supplied, to be used for human beings for a therapeutic purpose that does not achieve its primary intended action in or on the human body by pharmacological, immunological or metabolic means, but that may be assisted in its intended function by such means.
Medical Monitor	Medical monitors are a medically qualified individuals who review and evaluate information relevant to the safety of the investigational product throughout the development and implementation of the protocol.
Medsafe	The New Zealand medicines and medical devices safety authority
National Ethics Advisory Committee (NEAC)	The National Ethics Advisory Committee (NEAC) is a committee set up under New Zealand legislation to advise the Minister of Health on ethical issues in health services and research, and determine national ethical standards for the health sector. NEAC issues guidelines that set out the ethical standards that must be met by researchers when they undertake health and disability research. These guidelines are also used by ethics committees that review research study proposals – they are responsible for checking that each study meets the ethical standards set out in NEAC's guidelines.
Reference safety information (RSI)	All relevant safety information contained in the reference product information (e.g., CCDS) prepared by the marketing authorisation holder (MAH) and which the MAH requires to be listed in all countries where the company markets the drug, except when the local regulatory authority specifically requires a modification. It is a subset of information contained within the MAH's reference product information for the Periodic Benefit-Risk Evaluation Report (PBRER) Where the reference product information is the Company Core Data Sheet (CCDS), the reference safety information is the Company Core Safety Information (CCSI).
Safety critical adverse events	Adverse events and/or laboratory abnormalities identified in the protocol as critical to safety evaluations that should be reported to the sponsor according to the reporting requirements specified in the protocol.
Serious adverse Event (SAE)	A serious adverse event (experience) or reaction is any untoward medical occurrence that at any dose: - results in death, - is life-threatening, - requires inpatient hospitalisation or prolongation of existing hospitalisation, - results in persistent or significant disability/incapacity, or - is a congenital anomaly/birth defect.

Significant Safety Issue (SSI)	A safety issue that could adversely affect the safety of participants or materially impact on the continued 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.
Standing Committee on Therapeutic Trials (SCOTT)	A Committee of the HRC that undertakes scientific assessment of clinical trials and makes recommendations to the Director-General of Health on whether or not trials should be approved.
Standard Operating Procedure (SOP)	Detailed written instructions to achieve uniformity of the performance of a specific function and/or process(es).
Suspected Unexpected Serious Adverse Reactions (SUSAR)	A serious adverse reaction, the nature or severity of which is unexpected in that it is not consistent with the applicable product information (e.g., Investigator's Brochure for an investigational medicinal product).
Unanticipated Serious Adverse Device Effect (USADE)	Serious adverse device effect which by its nature, incidence, severity or outcome has not been identified in the current version of the risk analysis report.
Urgent Safety Measure (USM)	A measure required to be taken in order to eliminate an immediate hazard to a participant's health or safety.

1 Purpose

The regulatory requirements for clinical trials in New Zealand are outlined in <link to Guidelines on the Regulation of Therapeutic Products in New Zealand: Clinical trials – regulatory approval and good clinical practice requirements>.

This guidance document provides additional information on the requirements for safety monitoring and reporting for clinical trials involving **investigational medicinal products (IMPs)** and **investigational medical devices (IMDs)** in New Zealand.

In this document, 'investigational product' is used to refer to both IMPs and IMDs.

2 Introduction

Safety monitoring and reporting in clinical trials is performed to protect the participants in the trial from avoidable harm.

The nature and extent of participant safety monitoring should be based on a risk assessment of the trial intervention(s), the stage of the trial, and the extent of knowledge about the investigational products being tested.

Safety reporting encompasses a number of different activities including:

- reporting of individual case safety reports (ICSRs)
- reporting significant safety issues (SSIs)/urgent safety measures (USMs)

- periodic safety reporting
- reporting protocol amendments made for safety reasons.

In New Zealand, a number of different entities have roles and responsibilities with regard to safety monitoring and reporting in clinical trials. These include trial sponsors, investigators, clinical trial monitors, Medsafe, the Health and Disability Ethics Committee (HDEC), and institutions.

3 Responsibilities

Key safety monitoring and reporting responsibilities for trial sponsors, investigators, clinical trial monitors, Medsafe, the HDEC, and institutions are outlined below.

3.1 Sponsor

The sponsor has overall responsibility for the ongoing safety monitoring and evaluation of an investigational product.

Sponsors should establish appropriate safety monitoring processes based on the potential risks, size and complexity of a particular trial. For example, in trials with small numbers of participants (e.g. phase I trials), the nature, severity and frequency of risks may become more readily apparent through close monitoring of adverse events in individual participants, whereas in larger trials, risks may be better assessed through statistical comparisons of treatments.

Safety monitoring processes should be clearly documented in the trial protocol, including information on:

- the assessment and management of risk (if not in an alternative document)
- safety reporting definitions, procedures, responsibilities and reporting timelines
- any serious adverse events that do not require immediate reporting

Sponsors should evaluate all safety information that is available to them, including information reported by investigators and safety information from other sources. In the case of non-commercially sponsored trials, it is important that safety information is shared between the non-commercial sponsor and the manufacturer/supplier of the investigational product in order to ensure both parties satisfy their safety responsibilities.

To ensure there is appropriate independent oversight of safety within a clinical trial, sponsors should generally utilise an independent committee (eg, a Data and Safety Monitoring Committee (DSMC)) or independent individuals (eg, a Medical Monitor) to review accruing safety data.

Sponsors should:

- Assess and categorise the ICSRs received from investigators, and ensure that any reportable ICSRs are reported to Medsafe.
- Produce safety communications based on emerging safety data and feedback from DSMCs/medical monitors.
- Communicate safety information to investigators, Medsafe, and HDEC, and clarify the impact of each report on participant safety, trial conduct or trial documentation.

- Keep detailed records of all local AEs and all worldwide suspected unexpected serious adverse reactions (SUSARs) and maintain up-to-date tabulations and/or line listings to provide to Medsafe if requested.

Sponsors may be required to follow global company policies that mandate the reporting of ICSRs of SUSARs and six monthly line listings to investigators; however, this is not specifically required by this guidance.

Sponsors may delegate reporting responsibilities to third parties, for example, to a coordinating centre.

The requirements for sponsors reporting to Medsafe and HDEC are detailed further in section 4 and section 5 this guideline and are summarised in the Appendix. See also <link to Guidelines on the Regulation of Therapeutic Products in New Zealand: Clinical trials – regulatory approval and good clinical practice requirements>.

3.2 Investigator

Investigators (and principal investigators) should assess all local, site specific safety events and should act on any events as clinical care dictates. The role of the investigator with regard to safety reporting is to provide the sponsor with all relevant information so that an appropriate safety analysis can be performed.

Investigators should:

- Capture and assess all AEs that occur at the site as required and **in accordance with the protocol**.
- Report to the sponsor **within 24 hours** of becoming aware of the event:
    a. All SAEs, except those that are identified in the protocol as not needing immediate reporting
    b. Any occurrences of congenital anomaly/birth defect arising from any pregnancy of a participant (or partner)
    c. All urgent safety measures (USMs) instigated by the site
- Report to the sponsor **as specified in the protocol**:
    a. All safety critical adverse events
    b. Any additional requested information relating to reported deaths
- Report to the institution **within 72 hours** of becoming aware of the event:
    a. All significant safety issues (SSIs)
    b. All SUSARs arising from the local site

The reporting requirements for investigators are summarised in the Appendix. See also <link to Guidelines on the Regulation of Therapeutic Products in New Zealand: Clinical trials – regulatory approval and good clinical practice requirements>.

3.3 Clinical trial monitor

The clinical trial monitor (or clinical research associate) verifies that the rights, safety and wellbeing of participants are protected. This includes ensuring that adverse events are recorded, assessed, and reported in accordance with the protocol and regulatory requirements.

3.4 Medsafe

Medsafe is responsible for the regulatory control of therapeutic goods, including investigational products, in New Zealand. Medsafe administers the clinical trial approval process for trials involving IMPs, and the ongoing approval of trials in progress.

Medsafe must be kept informed by trial sponsors of any serious safety issues as they emerge. Medsafe may stop a trial by revoking consent at any time (eg, if there are significant concerns about participant safety).

The requirements for reporting to Medsafe are detailed further in section 4 and section 5 of this guideline. See also <link to Guidelines on the Regulation of Therapeutic Products in New Zealand: Clinical trials – regulatory approval and good clinical practice requirements>.

3.5 HDEC

HDECs check that proposed clinical trials meet established ethical standards that aim to protect participants. The safety monitoring and reporting arrangements for a trial must be sufficiently independent and appropriate for the specific features of a trial (eg, risk, size and complexity of the trial).

HDEC reviews the adequacy and completeness of the informed consent process and documentation in light of new information about risks and benefits. If new risks are identified that require a change to the participant information sheet/consent form, this requires submission of an amendment to the HDEC for approval. HDEC will assess whether changes to the risks or benefits of the investigational product or the trial conduct that are reported by the sponsor are compatible with continued ethical approval.

The requirements for reporting to HDECs are detailed further in section 4 and section 5 of this guideline. See also the Standard Operating Procedures for HDECs, Guidance on protocol deviation submissions and National Ethical Standards for Health and Disability Research and Quality Improvement.

3.6 Institution

An institution's responsibilities and oversight of safety information in clinical trials will differ depending on whether they are hosting externally sponsored clinical trials or sponsoring locally led non-commercial trials. In both cases they should help ensure that their site(s) understands and complies with sponsor requirements. Institutions should have oversight of any issues that may require management, such as disputes or litigation resulting from trials.

Where the institution is also named as the trial sponsor, the institution will also assume the sponsor responsibilities set out in this document.

Institutions should:

- Assess whether any safety reports received impact on medico-legal risk, the responsible conduct of research, adherence to contractual obligations or the trial's continued site authorisation and, where applicable, facilitate the implementation of corrective and preventative action.

Develop clear guidance for investigators detailing the requirements for safety reporting and monitoring in clinical trials. The guidance should cover the requirements for both externally sponsored clinical trials and, if applicable, internally sponsored investigator/initiated or collaborative group trials.

4 Safety Reporting for Trials Involving Medicines

4.1 Reporting adverse events/individual case safety reports

In New Zealand, sponsors are responsible for reporting adverse events associated with IMPs to Medsafe. The requirements for reporting are outlined below.

For adverse reactions associated with another supplier or manufacturer's medicine that is used as an active comparator in a clinical trial, sponsors must report such events to the manufacturer/supplier of the active comparator. There should be an agreement between the parties about who will be responsible for reporting to Medsafe.

HDEC does not require submission of ICSRs.

4.1.1 Expedited reporting of suspected unexpected serious adverse reactions

Serious adverse reactions occurring in clinical trial participants are considered unexpected if they are not outlined in the protocol and Investigator's Brochure and are not defined study endpoints.

Expedited reporting of fatal or life-threatening suspected unexpected serious adverse reactions (SUSARs) is required for some clinical trials. The requirements for reporting ICSRs of SUSARs depends on whether or not there is a pharmacovigilance system in place for the trial (see Box 1 and Box 2 below).

Box 1 – Reporting requirements when there is a pharmacovigilance system

If there is a pharmacovigilance system in place for the trial, expedited reporting of ICSRs of SUSARs occurring in New Zealand trial participants is **not required**. This is because sponsors operating a formal pharmacovigilance system are best placed to perform an analysis of these reports.

ICSRs of all SUSARs must be held in an accessible form and made available to Medsafe on request.

Details of the pharmacovigilance system should be included in the clinical trial application. Pharmacovigilance functions may be outsourced to a third party but the sponsor retains the overall responsibility for safety monitoring. For more information on pharmacovigilance systems, refer to the EMA ICH E2E Pharmacovigilance planning scientific guideline.

Reporting of SSIs/USMs and periodic safety reporting is still required as outlined in section 4.2 and section 4.3 of this guideline.

Box 2 – Reporting requirements when there is no pharmacovigilance system

If there is no pharmacovigilance system in place for the trial, the sponsor is required to report ICSRs of **all fatal or life-threatening SUSARs** occurring in New Zealand trial participants where the treatment is known (ie, unblinded). Blinding should be maintained for all other persons involved in the conduct or management of the trial, including those responsible for data analysis and/or interpretation of results. These reports should be submitted **within 15 calendar days** of the sponsor becoming aware of the event.

All other ICSRs of SUSARs occurring in New Zealand trial participants that are not fatal or life-threatening should not be routinely reported but must be held in an accessible form and made available to Medsafe on request.

If there is disagreement between a sponsor and an investigator as to whether a SUSAR has occurred (ie, where the sponsor's causality assessment conflicts with the assessment made by the investigator), the investigator's assessment cannot be downgraded by the sponsor (ie, altered from 'related' to 'not related'). In this case, if an investigator's judgment triggers the reporting of a SUSAR, the opinion of both the investigator and the sponsor should be provided with any SUSAR report sent to Medsafe.

4.1.2 Reporting other adverse events

The sponsor is expected to hold reports of all New Zealand AEs. These reports should not be routinely reported to Medsafe but must be held in an accessible form and made available to Medsafe on request.

Additionally, ICSRs of SUSARS occurring at overseas study sites should not be routinely reported to Medsafe but must be held in an accessible form and made available on request.

4.1.3 How to submit ICSRs

Reportable ICSRs can be submitted to Medsafe via:

- the CIOMS form through Ethics RM, or
- the CARM reporting webform.

If the webform is used, include the protocol number in the 'additional information' field on the last page of the form.

4.2 Reporting significant safety issues/urgent safety measures

Significant safety issues (SSIs) are issues that could adversely affect the safety of participants or materially impact on the continued ethical acceptability or conduct of the trial (eg, by altering the risk-benefit balance of the trial). In some cases SSIs may require urgent safety measures (USMs) to be taken by the sponsor and/or investigator to protect participants from an immediate hazard to their health and safety. Examples of SSIs include:

- A serious adverse event that could be associated with the trial procedures and that requires modification of the conduct of the trial

- A hazard to the patient population, such as lack of efficacy of an IMP used for the treatment of a life-threatening disease
- A major safety finding from a newly completed animal study (such as carcinogenicity)
- Recommendations of the Data Safety Monitoring Committee, relating to a participant safety issue, such as an increase in frequency or severity of an expected adverse reaction
- Safety issues resulting in a temporary halt or termination of a trial
- Single case events (e.g. toxic epidermal necrolysis, agranulocytosis, hepatic failure) requiring the implementation of urgent safety measures
- A serious breach of the clinical trial protocol or Good Clinical Practice (GCP) that is likely to significantly affect the safety of participants.

SSIs should be notified to Medsafe within **15 calendar days** of the sponsor becoming aware of the issue. The notification should include details of the issue (including if there have been any similar issues at overseas study sites) and proposed actions. Where a trial has been halted temporarily or terminated early due to safety reasons, the notification should include reasons for the halt/termination, the scope of the halt/termination, measures taken, and further actions planned. If a trial is being terminated or halted overseas, arrangements for halting the New Zealand arm of the study should be specified.

USMs may be instigated before being notified to Medsafe and HDEC. However, they must be reported to Medsafe and HDEC **as soon as possible**, but no later than **seven calendar days** after taking such measures.

SSIs/USMs should be reported through Ethics RM.

4.3 Periodic safety reporting

The Medicines Act mandates 6-monthly reporting of the progress of New Zealand clinical trials to be submitted by the sponsor to Medsafe, as detailed in <link to Guidelines on the Regulation of Therapeutic Products in New Zealand: Clinical trials – regulatory approval and good clinical practice requirements>. A detailed safety report should be submitted annually with one of the 6-monthly progress reports. The Development Safety Update Report (DSUR) may serve as the safety report. The DSUR does not need to be written specifically for New Zealand and the report submitted in other jurisdictions is acceptable. The timing of submission of a DSUR may be aligned with the reporting cycles of global companies. Refer to EMA (ICH E2F Development safety update report scientific guideline) and MHRA/Health Canada (Guideline on how to increase transparency when presenting safety information in the Development Safety Update Report (DSUR)) guidance for more information on the DSUR.

If a DSUR is not available, the safety report should generally include:

- A brief description and analysis of new and relevant safety findings.
- For IMPs not approved in New Zealand, a brief description and analysis of the safety profile of the IMP and its implications for participants, taking into account all available safety data and the results of other relevant clinical or non-clinical studies.
- A brief discussion of the implications of the safety data on the risks and benefits of the trial.
- A description of any measures taken or proposed to minimise risks.

Annual safety reports should be submitted to HDEC with the annual progress report every 12 months (from the date of approval), as detailed in the Standard Operating Procedures for HDECs. Annual safety reports for HDEC must be no longer than two pages and written in lay language. Line listings should not be included. The report should generally include a brief description and analysis of new and relevant findings, a brief discussion of the implications of safety data to the risk-benefit ratio for the trial and a description of any measures taken or proposed to minimise risks. A summary of the DSUR (ie, the executive summary) may serve as the annual safety report, accompanied by comments from the coordinating investigator in New Zealand.

Periodic safety reports should be submitted through Ethics RM.

4.4 Reporting trial amendments

All protocol amendments including safety-related changes should be submitted to Medsafe through Ethics RM for approval prior to implementation, as detailed in <link to Guidelines on the Regulation of Therapeutic Products in New Zealand: Clinical trials – regulatory approval and good clinical practice requirements>.

All substantial amendments should be submitted to HDEC for approval prior to implementation, as detailed in the Standard Operating Procedures for HDECs. A substantial amendment is defined as any amendment that is likely to affect to a significant degree the safety or physical or mental integrity of participants, the scientific value of the study, the conduct or management of the study, or the quality or safety of any medicine or item used in the study. Additionally, substantial deviations/violations of the clinical trial protocol and any serious or significant adverse findings identified in for-cause audit reports must be notified to HDEC in a timely manner, as outlined in the HDEC Guidance on protocol deviation submissions. Substantial protocol amendments, protocol deviations/violations, and adverse audit findings should be submitted through Ethics RM.

Note urgent safety measures (USMs) are considered to be a type of amendment, and these should be submitted for review as described in section 4.2 of this guideline.

5 Reporting for Trials Involving Medical Devices

Clinical trials involving IMDs are not regulated by the Medicines Act, therefore reporting of safety issues to Medsafe is preferred but not mandatory. HDEC reporting requirements apply for all clinical trials, including those involving IMDs.

5.1 Reporting individual case safety reports

The sponsor should assess and categorise the information received from investigators, and report all for fatal or life-threatening unanticipated serious adverse device effects (USADEs) occurring in New Zealand participants to Medsafe no later than **15 calendar days** after being made aware of the case. These can be reported via devices@health.govt.nz.

The sponsor is expected to hold reports of all New Zealand adverse device effects. These reports should not be routinely reported to Medsafe but should be held in an accessible form and made available to Medsafe on request.

HDEC does not require submission of ICSRs.

5.2 Reporting significant safety issues/urgent safety measures

The reporting criteria and timelines for SSIs/USMs relating to IMDs mirrors that of IMPs (see section 4.2 of this guideline for more information):

- SSIs should be notified to Medsafe within **15 calendar days** of the sponsor becoming aware of the issue.
- USMs should be notified to Medsafe and HDEC **as soon as possible**, but no later than **seven calendar days** after taking such measures.

Medsafe should be notified via devices@health.govt.nz.

HDEC should be notified via Ethics RM.

5.3 Periodic safety reporting

Annual safety reports should be submitted to HDEC with the annual progress report every 12 months (from the date of approval), as detailed in the Standard Operating Procedures for HDECs. Annual safety reports for HDEC must be no longer than two pages and written in lay language. Line listings should not be included. The report should generally include a brief description and analysis of new and relevant findings, a brief discussion of the implications of safety data to the risk-benefit ratio for the trial and a description of any measures taken or proposed to minimise risks. A summary of the DSUR (ie, the executive summary) may serve as the annual safety report, accompanied by comments from the coordinating investigator in New Zealand. These should be submitted through Ethics RM.

Periodic safety reports for trials involving IMDs do not need to be submitted to Medsafe.

5.4 Reporting trial amendments

All substantial amendments should be submitted to HDEC for approval prior to implementation, as detailed in the Standard Operating Procedures for HDECs. A substantial amendment is defined as any amendment that is likely to affect to a significant degree the safety or physical or mental integrity of participants, the scientific value of the study, the conduct or management of the study, or the quality or safety of any medicine or item used in the study. Additionally, substantial deviations/violations of the clinical trial protocol and any serious or significant adverse findings identified in for-cause audit reports must be notified to HDEC in a timely manner, as outlined in the HDEC Guidance on protocol deviation submissions. Substantial protocol amendments, protocol deviations/violations, and adverse audit findings should be submitted through Ethics RM.

Note urgent safety measures (USMs) are considered to be a type of amendment, and these should be submitted for review as described in section 5.2 of this guideline.

As clinical trials involving IMDs are not approved by Medsafe, protocol amendments should not be submitted to Medsafe.

6 Appendix

6.1 Summary of reporting requirements for sponsors

Table 1 Summary of sponsor reporting responsibilities for clinical trials of IMPs

Type	Action	Timeframe
Fatal or life threatening suspected unexpected serious adverse reactions (SUSARs) occurring in New Zealand study participants	If no pharmacovigilance system in place: Notify Medsafe	Within 15 calendar days of becoming aware of the event
	If pharmacovigilance system in place: Hold in accessible form to provide to Medsafe if requested	On request
All other SUSARs occurring in New Zealand study participants	Hold in accessible form to provide to Medsafe if requested	On request
All (overseas) SUSARs	Hold in accessible form to provide to Medsafe if requested	On request
Urgent safety measures (USMs)	Notify Medsafe, HDEC, and Investigators	As soon as possible, but no later than seven calendar days of taking such measures
All other significant safety issues (SSIs)	Notify Medsafe and Investigators	Within 15 calendar days of the sponsor becoming aware of the issue
Periodic safety updates	Notify Medsafe and HDEC	12-monthly safety report
Protocol amendments	Notify Medsafe and HDEC	Before implementation

6.2 Summary of reporting requirements for investigators

Table 2 Summary of investigator reporting responsibilities for clinical trials of IMPs

Type	Action	Timeframe
All adverse events (AEs)	Capture and assess all AEs occurring at the site	In accordance with protocol
All serious adverse events (SAEs) occurring at the site	Notify sponsor (except where SAEs have been identified in protocol as not requiring immediate reporting)	Within 24 hours of becoming aware of the event
Congenital anomalies/birth defects arising from any pregnancy (in site participant or partner)	Notify sponsor	
Urgent safety measures (USMs) instigated at the site	Notify sponsor	
All safety critical adverse events occurring at the site	Notify sponsor	In accordance with protocol
Additional information relating to reported deaths occurring at the site	Notify sponsor	
All significant safety issues (SSIs) occurring at the site	Notify institution	Within 72 hours of becoming aware of the event
SUSARs occurring at the site	Notify institution	

This guideline has been produced in collaboration with the New Zealand Association of Clinical Research (NZACRes)