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

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Contents

This guideline was produced by Medsafe in collaboration with
the New Zealand Association of Clinical Research (NZACRes)

Definitions

For a table of definitions, see Medsafe's *Guideline on the Regulation of Therapeutic Products in New Zealand*: *Clinical trials – Regulatory Approval and Good Clinical Practice Requirements* (abbreviated as *GRTPNZ: Clinical Trials*.) This document is published on the Medsafe website.

1 Purpose

This guidance document provides additional information on the requirements for safety monitoring and reporting for clinical trials of medicines and medical devices.

The full regulatory requirements for clinical trials in New Zealand are outlined in Medsafe's *GRTPNZ: Clinical Trials* (available on the Medsafe website).

2 Introduction

Safety monitoring and reporting in clinical trials helps to protect trial participants 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)/suspected unexpected serious adverse reactions (SUSARs)
- reporting significant safety issues (SSIs)/urgent safety measures (USMs)
- periodic safety reporting/Development Safety Update Reports (DSURs)
- reporting trial amendments made for safety reasons.

Section 30 of the Medicines Act 1981 (the Act) does not define who is responsible for safety monitoring and reporting in clinical trials in New Zealand. However, a number of different entities are involved, including trial sponsors, investigators, clinical trial monitors, Medsafe, the Health and Disability Ethics Committees (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 Trial sponsor

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

Trial 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 (eg, 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.

Trial 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 clinical trial safety, trial sponsors should generally utilise an independent committee (eg, an Independent Data Monitoring Committee [IDMC]) or independent individuals (eg, a medical monitor) to review accruing safety data.

Trial sponsors should:

- assess and categorise the ICSRs received from investigators (eg, assessing seriousness, causality, expectedness and categorising SUSARs)
- ensure that any reportable ICSRs are reported to Medsafe
- produce safety communications based on emerging safety data and feedback from IDMCs/medical monitors
- notify investigators, Medsafe, and HDEC of SSIs/USMs
- clarify the impact of the information on participant safety, trial conduct or trial documentation when communicating safety information to investigators, Medsafe, and HDEC
- keep detailed records of all local adverse events (AEs) and all worldwide SUSARs and maintain up-to-date tabulations and/or line listings to provide to Medsafe if requested.

The reporting requirements and timelines for trial sponsors are detailed further in section 4 and section 5 of this guideline and are summarised in Appendix 1.

Trial 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, Medsafe does not have this requirement.

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

3.2 Investigator

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 trial sponsor with all relevant information so that an appropriate safety analysis can be performed.

Investigators should do all of the following.

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

Appendix 1 has a summary of the reporting requirements for investigators.

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, regulatory requirements and good clinical practice (GCP).

3.4 Medsafe

Medsafe is responsible for the regulatory control of therapeutic products, including investigational products, in New Zealand. Medsafe administers the clinical trial approval process and the ongoing approval of trials in progress under section 30 the Act.

Trial sponsors must inform Medsafe about any serious safety issues as they emerge. Under section 30(8) of the Act, trial approval may be revoked at any time in writing (eg, if there are significant concerns about participant safety).

Section 4 and section 5 of this guideline detail the requirements for reporting to Medsafe.

3.5 HDEC

The HDEC checks 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).

The 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. The HDEC will assess whether the new information/changes are compatible with continued ethical approval.

Section 4 and section 5 of this guideline detail the requirements for reporting to the HDEC.

See also the HDEC documents:

- Standard Operating Procedures for HDECs
- Guidance on protocol deviation submissions
- 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, institutions should help to ensure that their site(s) understands and complies with the trial sponsor's 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 trial sponsor responsibilities set out in this document.

Institutions should do the following.

- 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 of Medicines

See Appendix 1 for a summary of reporting requirements for trial sponsors and investigators.

4.1 Reporting adverse events/individual case safety reports

In New Zealand, trial sponsors are responsible for reporting AEs associated with investigational products (IP) to Medsafe. The sections below outline the reporting requirements.

For AEs associated with another supplier or manufacturer's medicine that is used as an active comparator in a clinical trial, the trial sponsor should decide in advance whether such events should be reported to the other manufacturer/supplier and/or directly to Medsafe. Duplicated reporting to Medsafe (ie, reporting of the same event by both the sponsor and other supplier or manufacturer) should be avoided.

Events associated with a placebo will not usually meet the criteria for reporting to Medsafe. Adverse events associated with approved medicines used during a trial (eg, concomitant medicines, rescue medicines) should be reported as outlined in *GRTPNZ: Pharmacovigilance* (available on the Medsafe website).

HDEC does not require submission of ICSRs.

4.1.1 Expedited reporting of suspected unexpected serious adverse reactions (SUSARs)

SUSARs are serious adverse reactions, the nature or severity of which is unexpected in that it is not consistent with the applicable product information (eg, Investigator's Brochure for an investigational product).

Expedited reporting to Medsafe of ICSRs is required for **all fatal or life-threatening SUSARs** occurring in New Zealand trial participants where the treatment is known (ie, where a decision has been made to unblind). 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.

The trial sponsor should submit these reports within **15 calendar days** of becoming aware of the event, except in the circumstances outlined in '**Box 1 – When there is a pharmacovigilance system**'.

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

If there is disagreement between the trial 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 trial sponsor (ie, altered from 'related' to 'not related'). In this case, if an investigator's judgment triggers the reporting of a SUSAR, provide the opinion of both the investigator and the trial sponsor with any SUSAR report sent to Medsafe.

While pharmacovigilance functions may be outsourced to a third party, the trial sponsor retains the overall responsibility for safety monitoring and reporting.

Box 1 – When there is a pharmacovigilance system

Trial sponsors with established post-market pharmacovigilance systems that will be used to monitor the safety of the investigational product may choose not to submit expedited reports of SUSARs to Medsafe. This applies only where the trial sponsor holds all relevant safety information (ie, worldwide) for the investigational product, as these sponsors are best placed to perform an analysis of these reports.

The pharmacovigilance system should be consistent with international good pharmacovigilance practices (GVP; refer to *GRTPNZ: Pharmacovigilance* – available on the Medsafe website).

Key aspects of the pharmacovigilance system include (but are not limited to):

- access to pharmacovigilance expertise
- a quality system for managing pharmacovigilance processes and procedures
- a pharmacovigilance database for receiving, analysing and reporting ICSRs
- the ability to identify of new safety signals or trends from collected data
- the ability to produce DSURs (see section 4.3).

Where these requirements are met, and once a trial has been approved, notify Medsafe via email (askmedsafe@health.govt.nz) of the intention to not submit expedited reports of SUSARs for a clinical trial. Notification can occur at any time after the trial is approved.

Provide an overview or executive summary of the pharmacovigilance system with the initial notification. Notify Medsafe if subsequent trials use the same system, but details of the pharmacovigilance system do not need to be provided again. If there are significant changes to the pharmacovigilance system, notify Medsafe of these changes.

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

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

4.1.2 Reporting other adverse events

Medsafe expects the trial sponsor to hold reports of all AEs occurring in New Zealand participants. These reports should not be routinely reported to Medsafe (except when specified in section 4.1.1) but must be held in an accessible form and made available 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

Submit reportable ICSRs to Medsafe using the reporting methods outlined in section 4.4 of *GRTPNZ: Pharmacovigilance* (available on the Medsafe website). Include the trial protocol number in the report.

In addition the reporting methods outlined in *GRTPNZ: Pharmacovigilance*, reportable ICSRs may also be submitted via Ethics RM (using the relevant SCOTT post approval 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 the trial sponsor and/or investigator to take urgent safety measures (USMs) 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 investigational product 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 IDMC relating to a participant safety issue, such as an increase in frequency or severity of an expected adverse reaction
- single case events (eg, toxic epidermal necrolysis, agranulocytosis, hepatic failure) requiring the implementation of USMs
- a temporary halt or termination of a trial for safety reasons
- action that has been taken by another country's regulatory agency for safety reasons (relevant to the ongoing clinical trial in New Zealand).

Notify SSIs to Medsafe within **15 calendar days** of the trial sponsor's awareness 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 or mitigations. 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. If a trial is being restarted after a temporary halt, notify Medsafe and the HDEC before the study is restarted (approval is required before the study can restart).

USMs may be instigated before being notified to Medsafe and the HDEC. However, they must be reported to Medsafe and the HDEC **as soon as possible**, but no later than **7 calendar days** after taking such measures.

Report SSIs/USMs:

- through Ethics RM (using the relevant HDEC and SCOTT post approval forms), or
- to Medsafe by email at: askmedsafe@health.govt.nz.

4.3 Annual safety reporting

To Medsafe

Submit a safety report each year to Medsafe. If available, the DSUR can be the safety report (the DSUR executive summary is acceptable, with the full DSUR to be made available on request). The DSUR does not need to be written specifically for New Zealand and the report submitted in other jurisdictions is acceptable.

The timing of the DSUR submission may be aligned with the reporting cycles of global companies. Refer to ICH guidance (ICH E2F: Development Safety Update Report) for more information on the DSUR.

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

- a brief description and analysis of new and relevant safety findings
- a brief description and analysis of the safety profile of the investigation product and its implications for participants, considering 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.

The annual safety report may accompany one of the 6-monthly progress reports (progress reporting requirements are outlined in *GRTPNZ: Clinical Trials,* available on the Medsafe website). The DSUR may also serve as both the annual safety report and one of the two 6-monthly progress reports.

To HDEC

Submit the annual safety report 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
- must be written in lay language
- should 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
- should not include line listings.

The DSUR executive summary may serve as the annual safety report for HDEC, accompanied by comments from the coordinating investigator in New Zealand.

Submit annual safety reports through Ethics RM (using the relevant HDEC and SCOTT post approval forms).

4.4 Reporting trial amendments

Protocol amendments (including safety-related amendments) should be submitted to Medsafe, as detailed in *GRTPNZ: Clinical Trials* (available on the Medsafe website).

Submit substantial amendments 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 protocol deviations including any serious or significant adverse findings identified in for-cause audit reports must be notified to HDEC in a timely manner, as outlined in Guidance on protocol deviation submissions.

Submit substantial amendments/deviations through Ethics RM (using the relevant HDEC post approval form).

Urgent safety measures (USMs) are also a type of amendment. Submit USMs as described in section 4.2 of this guideline.

5 Reporting for Trials of Medical Devices

The Medicines Act 1981 does not regulate medical device trials (ie, clinical trials of investigational medical devices [IMDs]). Therefore, the following recommendations and timeframes for safety reporting to Medsafe are considered desirable but are not mandatory.

HDEC safety reporting requirements apply for all clinical trials, including medical device trials.

5.1 Reporting individual case safety reports

The trial sponsor should assess and categorise the information received from investigators and report all 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.

Report USADEs via email to: devices@health.govt.nz.

Medsafe expects the trial sponsor to hold reports of all New Zealand adverse device effects. These reports should not be routinely reported to Medsafe, but they should be held in an accessible form and made available 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 IPs (see section 4.2 of this guideline for more information).

- **SSIs**: notify Medsafe within **15 calendar days** of the sponsor becoming aware of the issue.
- **USMs**: notify Medsafe and HDEC **as soon as possible**, but no later than **7 calendar days** after taking such measures.

Notify Medsafe via email at: devices@health.govt.nz.

Notify HDEC via Ethics RM.

5.3 Periodic safety reporting

Submit annual progress reports (every 12 months from the date of approval) to HDEC, as detailed in the Standard Operating Procedures for HDECs. Submit reports through Ethics RM (using the relevant HDEC post approval form). A separate annual safety report is not required.

Medsafe does not require periodic reporting for medical device trials.

5.4 Reporting trial amendments

Submit all substantial amendments 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 protocol deviations including 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.

Submit substantial amendments/deviations through Ethics RM (using the relevant HDEC post approval form).

Urgent safety measures (USMs) are also a type of amendment. Submit USMs as described in section 4.2 of this guideline.

As Medsafe does not approve medical device trials, protocol amendments do not need to be submitted to Medsafe.

Appendix 1

Trial sponsors: Summary of reporting requirements

Table 1: Summary of trial sponsor reporting responsibilities for clinical trials of investigational products

Type	Action	Timeframe
Fatal or life threatening suspected unexpected serious adverse reactions (SUSARs) occurring in New Zealand study participants	Notify Medsafe	Within 15 calendar days of becoming aware of the event (except when Box 1 requirements are met)
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 7 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
Annual safety report	Notify Medsafe and HDEC	Annually
Progress report	Notify Medsafe and HDEC	6-monthly for Medsafe* Annually for HDEC
Protocol amendments	Notify Medsafe and HDEC	Before implementation

* As described in *GRTPNZ: Clinical Trials*, Section 30(7)(d)(ii) of the Medicines Act 1981 states importers or manufacturers must submit 6-monthly progress reports. We have included 6-monthly progress reports in this table for completeness. The importer or manufacturer may delegate the conduct of trial-related activities as necessary and in accordance with ICH E6(R3). The importer or manufacturer retains overall responsibility for the activities specified under section 30 of the Act.

Investigators: Summary of reporting requirements

Table 2 Summary of investigator reporting responsibilities for clinical trials of investigational products

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 trial sponsor	
Urgent safety measures (USMs) instigated at the site	Notify trial sponsor	
All safety critical adverse events occurring at the site	Notify trial sponsor	In accordance with protocol
Additional information relating to reported deaths occurring at the site	Notify trial sponsor	
All significant safety issues (SSIs) occurring at the site	Notify institution	Within 72 hours of becoming aware of the event (or as per institution requirements)
SUSARs occurring at the site	Notify institution	