ST VINCENT'S HOSPITAL
MELBOURNE
A FACILITY OF ST VINCENT'S HEALTH AUSTRALIA

RESEARCH GOVERNANCE UNIT
St. Vincent's Hospital (Melbourne)
Caritas Christi Hospice
St. George's Health Service
Prague House
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SAFETY REPORTING

Statement of Intent and Outcomes

The St Vincent's Hospital (Melbourne) Human Research Ethics Committee is committed to fulfilling Section 5 of The National Statement on Ethical Conduct in Human Research (2007 – Updated 2018) by ensuring.

Definitions

A serious adverse event includes any untoward medical occurrence that:

- results in death
- is life threatening
- requires in-patient hospitalisation or prolongation of existing hospitalisation
- results in persistent or significant disability/incapacity; or
- is a congenital anomaly / birth defect.

Procedure

The NHMRC guidance on *Safety monitoring and reporting in clinical trials involving therapeutic goods* (Nov 2016) and supplementary guidance on the *risk-based management and monitoring of clinical trials* (2018) is designed to clarify the responsibilities of all parties in relation to reports of adverse events (AE), including serious adverse events (SAEs) and suspected unexpected serious adverse reactions (SUSARs), occurring in clinical trials and where Human Research Ethics Committees (HRECs) have provided ethical approval.

Responsibilities of the Sponsor

Sponsors should establish safety monitoring processes that are based on the risk, size and complexity of the proposed research. In trials with small numbers of participants, e.g. phase I trials, risks may more readily become apparent through close monitoring of adverse events whereas in larger trials, risks are often better assessed through statistical comparisons of treatments. As such, sponsors should determine the most appropriate arrangements for ongoing monitoring and be prepared to justify these arrangements to the reviewing HREC.

Sponsors should evaluate all safety information that is reported by investigators as well as safety information from other sources. It is recognised that a non-commercial sponsor does not have access to all the safety data maintained by a commercial sponsor; however, non-commercial sponsors are responsible for evaluating all safety information available to them. To enhance the capacity of non-commercial sponsors to fulfil their responsibilities, entities that provide therapeutic goods to or receive therapeutic goods from other entities should share safety information with each other.

Sponsors should:

a) ensure that the trial protocol has clear sections describing:
   - the assessment and management of risk (if not in an alternative document)[1]
   - safety reporting definitions, procedures, responsibilities and reporting timelines.
   - any serious adverse events that do not require immediate reporting.

b) keep detailed records of all reported **adverse events (AEs)** and maintain up-to-date tabulations and/or line listings[2]

c) when communicating safety information to investigators and/or HRECs, clarify the impact of each report on patient safety, trial conduct or trial documentation

d) assess and categorise the safety reports received from investigators, and report all **suspected unexpected serious adverse reactions (SUSARs)** occurring in Australian participants to the Therapeutic Goods Administration
   - for fatal or life threatening Australian SUSARs, immediately, but no later than **7 calendar days** after being made aware of the case, with any follow-up information within a further 8 calendar days.
   - for all other Australian SUSARs, no later than **15 calendar days** after being made aware of the case.

Note 1: Sponsors may be required to follow global company policies that mandate the reporting of individual case SUSARs and six monthly line listings to investigators; however, this practice is not required by this guidance. Sponsors can discharge this responsibility by placing these reports on a portal or by sending them via e-mail. When the sponsor confirms that the report has no bearing on participant safety or trial conduct, confirmation of receipt of the communication may be requested, but there should be no requirement for investigators to print, review and file these reports.

Note 2: When determining whether a SUSAR has occurred, where the sponsor's causality assessment conflicts with the assessment made by the site investigator, the site investigator's assessment cannot be downgraded by the sponsor (i.e. 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 the TGA.

Note 3: When reporting a SUSAR to the TGA, the blind should generally[3] be broken by the sponsor. In order to avoid introducing biases, the blind 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.

e) review the investigator's brochure at least annually and update it when new and relevant information becomes available

[1] The trial protocol or an alternative document such as a safety monitoring plan, should also describe the composition, roles and responsibilities of oversight committees and plans for ongoing safety monitoring.
[2] The sponsor may be required to provide tabulations/line listings to the TGA on request.
[3] See Section D of ICH E2A: Managing Blinded Therapy Cases.

f) provide the HREC and investigators with any update/addenda of the investigator's brochure or where applicable, Product Information[4]

g) provide the HREC with an **annual safety report**[5] including a clear summary of the evolving safety profile of the trial. This report should allow the HRECs to assess whether ongoing safety monitoring is being conducted appropriately and that the trial's safety monitoring plans are being followed and where necessary, are being adapted to take into account new findings as the trial progresses

The annual safety report should generally include:

- a brief description and analysis of new and relevant findings
- for IMPs not on the Australian Register of Therapeutic Goods, a brief analysis of the safety profile of the IMP and its implications for participants taking into account all available safety data and the results of relevant clinical or non-clinical studies
- a brief discussion of the implications of the safety data to the trial's risk-benefit ratio
- a description of any measures taken or proposed to minimise risks

Note 1: The Executive Summary of safety information produced for international regulators, such as a *Development Safety Update Report (DSUR*), may serve as the annual safety report sent to HRECs (a full DSUR is not required). The timing of the annual safety report may be aligned with the reporting cycles of global companies or aligned with the annual progress report sent to the HREC.

Note 2: Where combination therapies are being investigated, options for annual safety reporting are described in Section 2.5 of the ICH Guideline E2F: Development Safety Update Report.

h) ensure that all sponsor responsibilities for safety monitoring and reporting (e.g. reporting SUSARs and significant safety issues to the TGA) are appropriately allocated or delegated

i) notify the TGA, HREC and investigators of all **significant safety issues (SSIs)** that adversely affect the safety of participants or materially impact on the continued ethical acceptability or conduct of the trial. Significant safety issues (SSI) that meet the definition of an urgent safety measure should be notified within **72 hours**, and all other significant safety issues should be notified within **15 calendar days** of the sponsor instigating or being made aware of the issue. Examples 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)
    - a temporary halt/termination of a trial for safety reasons

[4] When a Product Information is used in place of an investigator's brochure, any changes made by the Marketing Authorisation Holder should be reported to the HREC and investigators. Non-commercial sponsors should monitor for such changes.

[5] HRECs have the discretion to request more frequent reporting for specific trials, such as early phase trials.

- recommendations of the Data Safety Monitoring Board, where relevant for the safety of participants, such as an increase in frequency or severity of an expected adverse reaction
- single case events (e.g. toxic epidermal necrolysis, agranulocytosis, hepatic failure) that lead to an urgent safety measure.

Note 1: Often, significant safety issues (SSIs) do not fall within the definition of a SUSAR and thus are not subject to the reporting requirements for SUSARs. SSIs usually require other action, such as the reporting of an urgent safety measure, an amendment, a temporary halt or an early termination of a trial. In addition, SSIs often result in safety-related changes to trial documentation. These amendments should be submitted to the HREC **without undue delay**.[6]

Note 2: Urgent Safety Measures (USMs) are one type of significant safety issue where sponsors or trial investigators act immediately to protect participants from an immediate hazard to their health and safety. Consequently, USMs are often instigated before the TGA and HREC are notified. In these cases, it is strongly recommended that the sponsor **contact the TGA within 24 hours** of the measure being taken.

If this initial contact is by telephone, it should be followed-up with a written notification provided by facsimile or e-mail within 72 hours. Table 1 illustrates the types of action that result from SSIs and the associated timelines for **written notification.**

Table 1: Sponsor Reporting of Significant Safety Issues

Action	What is communicated	Recipients	Timelines and further review
a. Urgent safety measure (USMs)[15]	• Reasons for the urgent safety measure • Measures taken • Further actions planned	Notify the TGA, investigators and the HREC	Without undue delay and no later than **72 hours** of the measure being taken. The HREC is not required to approve USMs but may consider whether any proposed actions are appropriate, such as the submission of an amendment relating to revised trial documentation.
b. Notification of an amendment	• Details of the significant safety issue • Further actions planned	Notify the TGA[16], investigators and the HREC	Without undue delay and no later than **15 calendar days** of the sponsor becoming aware of the issue. Sponsors should submit to the HREC an amendment relating to any revised trial documentation, **without undue delay**.
c. Temporary halt of a trial for safety reasons[17]	• Reasons for the halt • The scope of the halt (e.g. suspension of recruitment or cessation/interruption of trial treatment) • Measures taken • Further actions planned	Notify the TGA, investigators and the HREC	Without undue delay and no later than **15 calendar days** of the sponsor's decision to halt the trial. Where it is necessary to seek ethical review of related actions (e.g. informing participants or arranging continuing care and follow-up), a letter describing these actions should be submitted to the HREC within **15 calendar days** of the temporary halt

6 Good Clinical Practice requires sponsors, through their investigators, to inform participants of new safety information in a timely fashion
15 Temporary halts/early terminations implemented as urgent safety measures (USM) should be notified within USM timeframes.
16 The TGA should receive notification that a SSI has occurred but the amendment revising trial documentation does not require submission to the TGA.
17 Both the TGA and the HREC should be notified if the trial restarts, including evidence that it is safe to restart.

d. Early termination of a trial for safety reasons	• Reasons for the early termination • Measures taken • Further actions planned	Notify the TGA, investigators and the HREC	Without undue delay and no later than **15 calendar days** of the sponsor's decision to terminate the trial. Where it is necessary to seek ethical review of related actions (e.g. informing participants or arranging continuing care and follow-up), a letter describing these actions should be submitted to the HREC within **15 calendar days** of the early termination.

Responsibilities of the Principal Investigator

Investigators should assess[7] all local 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.

The Principal Investigator should:

a) capture and assess all AEs that occur at the site as required and in accordance with the protocol
b) report to the 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)[8]
   - all urgent safety measure instigated by the site
c) report to the sponsor as specified in the protocol:
   - all safety critical events
   - any additional requested information relating to reported deaths
d) report to the institution **within 72 hours** of becoming aware of the event:
   - all significant safety issues
   - SUSARs[9] arising from the local site **(should be reported to the local governance office where the SUSAR arises)**.

Responsibilities of the HREC

The sponsor, through their independent safety monitoring arrangements, has the primary responsibility for monitoring the ongoing safety of the investigational medicinal product. The HREC should be satisfied that the sponsor's arrangements are sufficiently independent and commensurate with the risk, size and complexity of the trial.

The approving HREC should:

[7] Causality assessment decisions should be made by a qualified physician, or when appropriate, a qualified dentist.
[8] Processes for handling consent for follow-up of participants (or pregnant partners of participants) should be in place.
9 Reported when, in the investigator's judgement, a SUSAR has occurred. The investigator should not unblind the SUSAR for the purposes of reporting to their institution.

a) assess the safety of proposed trials, including whether the evaluation of the anticipated benefits and risks is satisfactory and ensure that the sponsor has proportionate systems in place to mitigate and manage any identified risks
b) satisfy itself that the sponsor's ongoing safety monitoring arrangements are adequate, including the justification for appointing/not appointing a Data Safety Monitoring Board and any 'stopping rules' or criteria for withdrawing individual participants from the trial
c) keep under review the adequacy and completeness of the informed consent process and documentation in the light of new information about risks and benefits
d) assess whether changes to the risk-benefit ratio that are reported by the sponsor are compatible with continued ethical approval[10]
e) advise the TGA, investigators and their institutions of any decision to withdraw approval

Note: While HRECs must keep approvals under review in light of safety information it receives, the responsibility for proactively monitoring the ongoing risk-benefit ratio of the trial remains with the sponsor at all times.

Responsibilities of the 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.**

The Institution should:

a) 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
b) develop clear guidance for investigators detailing the requirements for safety reporting and monitoring in clinical trials. This document(s) should cover the requirements for both externally sponsored clinical trials and, if applicable, internally sponsored investigator/initiated or collaborative group trials.

For investigator-initiated studies where St Vincent's Hospital Melbourne (SVHM) is assuming the sponsor responsibilities, the investigator(s) should:

If an event is Related, Possibly Related or Probably Related - Report immediately (within 24 hours of learning of the event) to the sponsor (in this case SVHM) all serious adverse events (SAEs) except for those SAEs that the protocol or other documents (e.g. investigator's brochure) identifies as not needing reporting. If the event is Unrelated a report should be submitted within 7 days of learning of the event. The template to be used is publically available on the Research Governance Unit Website and should be submitted electronically to SAE.ClinicalTrial@svha.org.au

[10] An HREC may discuss any concerns it has with any aspect of a clinical trial with the TGA.

Ensure that the immediate and follow-up reports identify subjects by unique code numbers assigned to the trial subjects rather than by the subjects' names, personal identification numbers, and/or addresses.
All submissions will be reviewed by the Chair of the HREC, and formally acknowledged in writing. If the Ethics Committee requires subsequent action, investigators will be notified.

Comply with the applicable regulatory requirement(s) related to the reporting of unexpected serious adverse drug reactions to the sponsor.

Ensure that adverse events and/or laboratory abnormalities identified in the protocol as critical to safety evaluations are reported to the sponsor according to the reporting requirements and within the time periods specified by the sponsor in the protocol.

Ensure that for reported deaths; supply sponsor with any additional requested information (e.g., autopsy reports and terminal medical reports).

Record non-serious and expected adverse reactions and adverse events as part of GCP. It is imperative that, in accordance with GCP principles, an internal statistical analysis of these data is performed. The sponsor should be advised of any safety issues which emerge during this process. Such data do not need to be submitted on a routine basis to the sponsor during the trial, but should be available for submission to the sponsor *on request*, and where applicable, submitted as part of an application for registration.

Notify the sponsor of SAEs, in line with institutional procedures and as per any specific ethics approval conditions related to the particular study.

Notify the sponsor of any information received from the study that may be new and have an impact on the continued ethical acceptability of the trial, or may indicate the need for amendments to the trial protocol, including monitoring of safety.

Reports of serious adverse events, or which relate to a claim made against the Hospital/Institution or a member of its staff and/or the occurrence of circumstances which may subsequently give rise to a claim against the Hospital/Institution, must be reported to VMIA in accordance with the provisions of the VMIA Public Liability and Medical Indemnity Policies. Failure to give proper, prompt notification of any circumstances likely to give rise to a claim or the making of a claim may compromise insurance coverage for the Hospital/Institution and/or a member of its staff.

Serious Adverse Events which are possibly, probably or definitely related to the drug/device, or which require a change to the Participant Information and Consent Form or the conduct of the Trial should be promptly notified to the VMIA.

References

- National Health and Medical Research Council (2016). Guidance: Safety monitoring and reporting in clinical trials involving therapeutic goods.
- The National Statement on Ethical Conduct in Research Involving Humans in accordance with the NHMRC Act, 2007 – updated 2018

- Australian Code for the Responsible Conduct of Research (2018)

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