

Alfred Hospital Ethics Committee

SAFETY MONITORING AND REPORTING REQUIREMENTS

The NHMRC *Safety monitoring and reporting in clinical trials involving therapeutic goods* (November 2016)¹ guidance document advocates risk-adapted safety monitoring arrangements to be commensurate to the risk, size and complexity of the trial taking into account factors such as the risks of the intervention relative to standard of care and the information available about the investigational product. The Alfred Hospital Ethics Committee adopts the requirements set out in the Guidance with the following refinements and clarifications:

1. Scope of the guidance

Whilst the guidance document specifically refers to clinical trials involving therapeutic goods, it should be adopted for all interventional studies submitted to the Alfred Hospital Ethics Committee for review.

2. Responsibilities of the Sponsor, Principal Investigator, HREC, Institution and TGA

Whilst it is the responsibility of the Principal Investigator to capture, assess and report all adverse events to the Sponsor and the Institution in accordance with the Protocol and local requirements, it is the Sponsor who has the primary responsibility of evaluating the safety information obtained from investigators and other sources and to communicate this information and its impact on patient safety, trial conduct or trial documentation to investigators, HRECs and the TGA as required.

The role of the HREC is to assess the adequacy of the Sponsor's safety monitoring arrangements with respect to the risk, size and complexity of the trial and to evaluate these in light of new information about the risks and benefits. If the institution is also the sponsor of the study, it assumes the obligations of the sponsor. If this is not the case, the role of the institution is to evaluate whether any safety information impacts on medico-legal risk, the responsible conduct of the research or continued site authorisation of the trial. Alfred Health's requirements are detailed on the Ethics & Research Governance website. The TGA retains the responsibility of regulatory control of therapeutic goods.

3. Preparation of a safety monitoring plan

All new applications submitted to the Ethics Committee will need to include in the protocol a safety monitoring plan which clearly describes:

- The assessment and management of risk
- Safety reporting definitions, procedures, responsibilities and reporting timelines, including where relevant, notifying the TGA
- Any serious adverse events that do not require immediate reporting
- The composition, roles and responsibilities of oversight committees set out in a committee charter
- Plans for ongoing safety monitoring

Researchers must ensure that the action they take to manage, monitor and report adverse or unforeseen events accords with the procedures detailed in the protocol and ethics submission for that project.

4. New terminology – Significant safety issues (SSIs) and urgent safety measures (USMs)

There is no longer the requirement to submit individual reports of adverse events (AEs), serious adverse events (SAEs), suspected unexpected serious adverse reactions (SUSARs) and unanticipated serious adverse device effects (USADEs) to the Ethics Committee. Instead, apart from any additional

reporting requirements imposed by the Ethics Committee, only events that meet the criteria of a significant safety issue (SSI) and/or an urgent safety measure (USM) are to be reported to the Committee.

Urgent safety measures (USMs) required to be taken in order to eliminate an immediate hazard to a participant's health or safety **that occur in either a site for which the Ethics Committee is responsible or externally**, must be reported to the Alfred Ethics & Research Governance Office **within 72 hours** of knowledge of the event.

Other significant safety issues (SSIs), which could be in the form of AEs, SAEs, SUSARs or USADEs that could adversely affect the safety of participants or materially impact on the continued acceptability or conduct of the trial or result in a temporary halt/termination of a trial or require an amendment **and that occur in either a site for which the Ethics Committee is responsible or externally**, must be reported to the Alfred Ethics & Research Governance Office **within 15 calendar days** of the sponsor instigating or being made aware of the issue. Resultant amendments should be submitted without undue delay. All reports should be submitted on the Victorian DHHS Safety Report form and must include sufficient information and context.

The Adverse Event Flowchart depicts the reporting requirements.

5. Reports from Data Safety Monitoring Boards (DSMBs) and/or Safety Monitors

Researchers are required to request reports from data and safety monitoring boards or other safety monitors for studies approved by the Alfred Hospital Ethics Committee. The timing of these reports should be in accordance with any monitoring and reporting arrangements requested/approved by the Alfred Hospital Ethics Committee for that project. The reports should be forwarded promptly to the Alfred Health Ethics and Research Governance Office.

6. Updated Investigator's Brochures (IBs), Product Information (PI) and Development Safety Update Reports (DSURs)

Updated IBs (if not part of an amendment) or Product Information, where applicable, or the executive summary of DSURs should be forwarded by the Co-ordinating Principal Investigator (streamlined application) or the Alfred Health Site Principal Investigator (single site application) to the Alfred Health Ethics and Research Governance Office on receipt from the sponsor, with the following core documents:

- a. Full revised IB or PI and a summary of changes (if not included in the revised IB or PI) or executive summary of the DSUR
- b. The Victorian DHHS amendment request form which includes an impact statement from the Principal Investigator (advising whether, or not, the changes may have an impact on study participants) in the 'Description of changes' field in the form.

7. Annual Safety Report

The annual safety report should be submitted by the Co-ordinating Principal Investigator (streamlined application) or the Alfred Health Site Principal Investigator (single site application) to the Alfred Health Ethics and Research Governance Office on receipt from the sponsor. **The Alfred Hospital Ethics Committee has the discretion to request more frequent reporting for specific trials.** The information to be included in the annual safety report is specified in the Guidance.

The reports should be accompanied by a statement from the Principal Investigator advising whether, or not, there may be any impact on study participants. The Victorian Department of Health and Human Services Annual Safety Report form can be used as the annual safety report. The DSUR

Executive Summary is not considered appropriate as it does not meet the requirement of providing a clear summary of the evolving safety profile of the trial.

The annual safety report is to be submitted once the Sponsor makes it available to the researchers. Researchers will be asked to declare in the annual progress report whether the annual safety report has been provided during the previous 12 months and if not, should be submitted with the progress report.

8. Effective date of the adoption of the Guidance

The new Guidance in relation to the submission of a safety monitoring plan will be adopted for studies submitted for review by the Ethics Committee on or after 1 November 2017. However, all current open interventional studies will be required to report in accordance to the 2016 Guidance document

Professor John McNeil
Chair, Alfred Hospital Ethics Committee
October 2017

References:

1. National Health and Medical Research Council (2016). Guidance: Safety monitoring and reporting in clinical trials involving therapeutic goods. Canberra: National Health and Medical Research Council:
https://www.nhmrc.gov.au/files/nhmrc/file/publications/16469_nhmrc_-_ahec_position_statement-web.pdf

Glossary of Acronyms and Terms

| Acronym | Terms and Definitions |
|--------------|---|
| AE | Adverse event: Any untoward medical occurrence in a patient or clinical trial participant administered a medicinal product and that does not necessarily have a causal relationship with this treatment. |
| DSMB | Data Safety Monitoring Board: The committee which oversees the data collected in a clinical trial and makes decisions about the ongoing acceptability of a trial. |
| DSUR | Development Safety Update Report |
| HREC | Human Research Ethics Committee |
| IB | Investigator's Brochure |
| NHMRC | National Health and Medical Research Council |
| PI | Product Information |
| SAE | Serious Adverse Reaction: Any adverse event/adverse reaction that results in death, is life-threatening, requires hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, or is a congenital anomaly or birth defect. |
| SSI | Significant Safety Issue: A safety issue that could adversely affect the safety of participants or materially impact on the continued ethical acceptability or conduct of the trial. |
| SUSAR | Suspected Unexpected Serious Adverse Reaction: An adverse reaction that is both serious and unexpected. |
| TGA | Therapeutic Goods Administration |
| USADE | Unanticipated Serious Adverse Device Effect: 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. |
| USM | Urgent Safety Measure: A measure required to be taken in order to eliminate an immediate hazard to a participant's health or safety; is a type of SSI. |