Purpose

To outline the requirements for safety reporting to Bellberry HRECs. Bellberry follows the requirements of the National Statement on Ethical Conduct in Human Research (2007 incorporating all updates) and the NHMRC Guidance: 'Safety monitoring and reporting in clinical trials involving therapeutic goods (November 2016)'.

Definitions

Annual Safety Report (ASR): Is a document regarding the monitoring and evaluation of the evolving safety profile of the Investigational Medicinal Product (IMP) and the mitigation of potential risks. Please see NHMRC Guidance (p.8) for general requirements.

Data safety monitoring board (***DSMB):*** An independent and multidisciplinary group established by the trial sponsor to review, at intervals, accumulating trial data, in order to monitor the progress of a trial and to make recommendations on whether to continue, modify or stop the trial for safety or ethical reasons.

Development Safety Update Report (DSUR): Is the pre-marketing equivalent of the post-marketing Periodic Safety Update Report (PSUR). It covers drugs, biological, vaccines and combo products. It is a stand-alone document that is not just a data dump but is an analytical document.

Investigator Brochure (IB): The document containing a summary of the clinical and non-clinical data relating to an investigational medicinal product that are relevant to the study of the product in humans.

Investigational Device (ID): Any instrument, apparatus, implement, machine, appliance, implant, software, material or other similar or related article.

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 a product with a marketing authorisation when used or assembled (formulated or packaged) in a way different from the approved form, or when used for an unapproved indication, a new patient group or when used to gain further information about an approved use.

Serious Adverse Event (SAE), Serious Adverse Reaction (SAR): An event/reaction that: results in death; is life threatening; requires hospitalisation/prolongation of existing hospitalisation; results in persistent or significant disability or incapacity; is a congenital anomaly or 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. The Sponsor is responsible for determining the significance and the actions taken. The exception to this rule is USMs initiated by the Investigator. SSIs usually require 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.

Urgent Safety Measure (USM): A measure required to be taken in order to eliminate an immediate hazard to a participant's health or safety. Note: This type of significant safety issue can be instigated by either the investigator or sponsor and can be implemented before seeking approval from HRECs or institutions.

An urgent safety measure is also an event that requires a change to trial procedures or the addition of unapproved trial procedures which are not defined in the protocol. Therefore, where urgent interventions are managed in accordance with the protocol, they are not considered USMs. For example, an investigator may implement an immediate IMP dose reduction, in response to an observed toxicity, in accordance with the protocol's dose modification rules.

Guidance

Please see Appendix 1 for Safety documentation/submission requirements.

Responsibility of Sponsor: In line with ICH GCP and ISO 14155 the NHMRC guidelines place the responsibility for the ongoing safety evaluation of the investigational product and Clinical investigation of medical devices with the sponsor. To ensure that there is appropriate independent oversight of safety within a clinical trial, sponsors should generally utilise an independent committee or independent individuals to review accruing safety data. It is the outcome of these reviews that are required to be provided to the HRECs, investigators, institutions, and the Therapeutic Goods Administration (TGA).

Sponsors evaluate all safety information from the investigators and other sources and are responsible for generating the safety communications. The communication of the safety information to investigators and HRECs also needs to include any clarification of the impact of each report on participant safety, trial conduct or trial documentation. If there is no significant impact, then (consistent with the definition of an SSI) the issue is unlikely to be reportable to either investigators or HREC.

Responsibility of the Principal Investigator: Investigators should assess all local safety events and should act on any events as clinical care dictates. Causality assessment decisions should be made by a qualified physician. 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. A detailed explanation of the responsibilities can be found in the NHMRC guidance document 'Safety Monitoring and Reporting in Clinical Trial Involving Therapeutic Goods'. In the first instance, Bellberry requires that all applications, including safety reporting, be submitted through eProtocol by the Investigator, as prompted by the Sponsor.

In the event of urgent submissions relating to participant safety, persons unable to submit via eProtocol can do so via bellberry@bellberry.com.au with the subject title stating the HREC ID.

Responsibility of the HREC & potential HREC actions: 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 Chair of the HREC will take whatever actions are deemed necessary to address the unanticipated safety issue(s). Examples of actions that might be taken include, but are not limited to: suspension of all or parts of the research; termination of the research; notification of previously enrolled and/or currently enrolled subjects of new information; require modifications to the informed consent; require modifications to the protocol when permissible; require the investigator to re-consent enrolled subjects; increase monitoring of subjects; increase frequency of continuing review; observation or monitoring of the research; require additional training and education; referral to other organisational entities.

After review by the HREC Chair/and delegates, the HREC will indicate their determination in writing to the investigator within a reasonable timeframe, but no later than 10 business days of the determination.

When the HREC determines that an unanticipated safety issue or serious or continuing non-compliance has occurred, and the HREC suspends or terminates approval of research, the outcome of the HREC's actions will be reported to the appropriate Institutional officials and government departments or agency heads.

References

National Statement on Ethical Conduct in Human Research (2007 incorporating all updates)
NHMRC Safety Monitoring and Reporting in Clinical Trials (2016) & Data Safety Monitoring Boards (2018)
ISO 14144:2011 Clinical Investigation of medical devices for human subjects - GCP
MAR SOP2.1 Review of Safety Reporting
MAR F2.1.1 Safety Reporting (application questions)

Appendix 1: Safety Documentation/Submission Requirements

This table has been adapted from the NHMRC Safety Monitoring and Reporting in Clinical Trials (November 2016)' to inform the investigator of the HREC reporting responsibility. Please note, the HREC does not require the submission of Six-Monthly Line Listings or individual SAEs that do not meet the SSI definitions below.

Submission type	What is communicated[1]	Timelines and further review
SSI: Urgent safety measure (USMs)	• Reasons for the urgent safety measure • Measures taken[2] and further actions planned	• Without undue delay and no later than 72 hours of the measure being taken.[3] • 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.[4]
SSI: Notification of an amendment	• Details of the significant safety issue • Further actions planned	• Without undue delay and no later than **15 calendar days** of the sponsor becoming aware of the issue. • Submit to the HREC an amendment relating to any revised trial documentation,[4] **without undue delay.**
SSI: Temporary halt of a trial for safety reasons/Early termination of a trial for safety reasons	• Reasons for the halt/early termination • The scope of the halt (e.g., suspension of recruitment or cessation/interruption of trial treatment) • Measures taken and further actions planned	• Without undue delay and no later than **15 calendar days** of the sponsor's decision to halt the trial/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 temporary halt/early termination.
Annual safety report/DSUR	• The Executive Summary of safety information produced for international regulators, such as a DSUR, may serve as the annual safety report sent to HRECs.	• Report to HREC within a reasonable time frame. • 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.
DSMB letters, charter, TOR, outcomes	• Document in format determined by the sponsor	• Report as per the caveat requirement on the approval letter.[5]
Investigator Brochure update	• Any update/addenda of the investigator's brochure or where applicable, Product Information[6]	• Report to HREC as and when updates are generated.[6] • Review the investigator's brochure at least annually and update it when new and relevant information becomes available.

1. If the application is multi-centre, please also respond on behalf of additional sites in your submission.
2. Comment on the site's implementation of the USM, including how many participants are impacted and the plan for implementing the action items.
3. The date of 'receipt of notification from sponsor to sites' can be substituted for the date of the 'measure being taken.'
4. Please submit any revised trial documentation or new participant-facing documents, as a result of the SSI, via an amendment.
5. Only required if the HREC requests it via a caveat on their approval letter or if a Sponsors' policy requires the submission.
6. If an updated Investigator's Brochure (IB) has been identified in the DSUR, the IB may be requested via a cycle of comments or a note on the acknowledgement letter. Please submit any IB updates via an amendment.