Guidelines for Research Safety Monitoring and Reporting

Barwon Health

In November 2016, the NHMRC revised its guideline for Safety Monitoring and Reporting of research.

The recently released document, 'Safety Monitoring and reporting in clinical trials involving therapeutic goods' is designed to clarify the responsibilities of all parties in relation to safety monitoring and reporting of all adverse events occurring in clinical trials.

In summary, the key change in the revised guideline places the **responsibility for safety monitoring and reporting requirements with the sponsor** of a clinical trial, defined as 'an individual, organisation or group taking on responsibility for securing the arrangements to initiate, manage and finance a study'. A sponsor should be identified for all clinical trials and all sponsor functions, including safety monitoring and reporting should be clearly allocated or delegated. The guideline advises that, to ensure appropriate independent oversight of safety within a clinical trial, sponsors should utilise an independent committee or independent individuals (e.g. Data Safety Monitoring Boards, or a medical monitor) to review accruing safety data. The outcome of these reviews should be provided to the HRECs, Investigators, Institutions and as requested, the Therapeutic Goods Administration (TGA).

To reflect the updated NHMRC guideline, Barwon Health has also revised its advice to researchers and provides the following summary to clarify the role of all research stakeholders in addressing the monitoring, collection and reporting of adverse events that occur in clinical trials involving investigational medicinal products (IMPs) and investigational medical devices (IMDs).

Deviations and Breaches

There have been changes to the reporting of protocol deviations and breaches after the NHMRC released additional guidance for **Reporting of Serious Breaches of Good Clinical Practice (GCP) or the Protocol for Trials Involving Therapeutic Goods** in 2018. This guidance applies to both commercial and non-commercial clinical trials involving therapeutic goods.

HRECs now only need to be made aware of the small sub-set of deviations that have a significant impact on the continued safety or rights of participants or the reliability and robustness of the data generated in the clinical trial. This is what we call 'serious breaches'. Serious breaches occurring at a site should also be reported by the investigator to their institution, as they may impact on medico-legal risk, the responsible conduct of research, or adherence to contractual obligations.

Table 1: Definitions

RGO	Research Governance Officer
HREC	Human Research Ethics Committee
DSMB	Data Safety Monitoring Board
DSUR	Data Safety Update Report
VMIA	Victorian Managed Insurance Authority
AE - Adverse Event	Any untoward medical occurrence, unintended disease or injury in a participant administered a medicinal product/device and that does not necessarily have a causal relationship with this treatment/device
AR - Adverse Reaction	Any untoward and unintended response to an investigational medicinal product related to any dose administered
IB – Investigators Brochure	Compilation of the current clinical and non-clinical information on the IMP/IMD relevant to the study of the product/device in humans
SAE – Serious Adverse Event **SAR – 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
SUSAR - Suspected Unexpected Serious Adverse Reaction	An adverse reaction that is both serious and unexpected
USADE- Unanticipated Serious Adverse Device Effect	A serious adverse device effect that by its nature, incidence, severity or outcome has not been identified in the risk analysis report
SSI Significant Safety Issue (Refer to Table 4)	A safety issue that could adversely affect the safety of participants or materially impact on the continued ethical acceptability or conduct of the trail (can include USM)
USM - Urgent Safety Measure (Refer to Table 4)	A measure required to be taken in order to eliminate an immediate hazard to a participant's health or safety (Instigated by PI OR Sponsor)
Protocol Deviation/Non Serious Breach	A Deviation is any breach, divergence or departure from the requirements of Good Clinical Practice (GCP) or the clinical trial protocol and <u>does not affect</u>; - The safety or rights of a trial participant - The reliability and robustness of the data generated in the clinical trial
Serious Breach	Breach of GCP or the protocol that is likely to affect to a significant degree; - The safety or rights of a trial participant - The reliability and robustness of the data generated in the clinical trial
Suspected Breach (Third Party)	A report that is judged by the reporter as a possible serious breach but has yet to be formally confirmed by the sponsor

Sponsor Responsibilities

Main role: Establish appropriate safety monitoring processes based on the risk, size and complexity of the trial and justify these to the HREC and evaluate all safety information reported

As per NHMRC Safety Monitoring and Reporting Guidelines (a – i) pg. 7-9

- When communicating safety information to Investigators and/or HRECs, sponsors must clarify the impact of each report on patient safety, trial conduct or trial documentation

As per NHMRC Reporting of Serious Breaches of Good Clinical Practice (GCP) or the Protocol for Trials Involving Therapeutic Goods (pg. 3)

- Sponsors have primary responsibility for determining whether any suspected breach meets the definition of a serious breach. The judgement on whether a serious breach is likely to have significant impact on the reliability and robustness of trial data should be made by the sponsor. If the sponsor is unsure whether a potential serious breach has significant impact on the rights or safety of participants they should contact the reviewing HREC for advice.

Where Barwon Health is the sponsor of Investigator Initiated research projects, the institution has delegated this responsibility (regarding safety monitoring and reporting only) to the Coordinating Principal Investigator – *please refer to Table 3 and Table 4 for safety reporting requirements for Principal Investigators with sponsor responsibilities.*

Principal Investigator Responsibilities

Main role: To provide the sponsor with all relevant information so that an appropriate safety analysis can be performed

As per NHMRC Safety Monitoring and Reporting Guidelines (a – d) pg 10

Please refer to Table 2 for safety reporting requirements for Investigators

HREC Responsibilities

Main role: To be satisfied that the sponsor's arrangements are sufficiently independent and commensurate with risk, size and complexity of the research. To review safety monitoring reports provided by the study sponsor.

As per NHMRC Safety Monitoring and Reporting Guidelines (a – e) pg 10-11

- Barwon Health HREC advises that all Investigator Initiated Clinical Trials should have appropriate independent oversight of safety and should utilise an independent committee or independent individual (e.g. Data Safety Monitoring Boards, or a medical monitor) to review accruing safety data. Membership and meeting timelines for DSMBs must be provided with ethics submission.

Institution Responsibilities

Main role: To ensure that all Barwon Health researchers understand and comply with their roles and responsibilities for safety reporting and monitoring and that of the Study sponsor, as set out in the NHMRC guidelines.

As per NHMRC Safety Monitoring and Reporting Guidelines (a – b) pg 11

Note: Reporting to VMIA is an institutional responsibility

TGA Responsibilities

Main role: Regulatory control of therapeutic goods in Australia

As per NHMRC Safety Monitoring and Reporting Guidelines (a – b) pg 11

Safety Reporting Responsibilities

Table 2: Safety reporting requirements for Barwon Health Principal Investigators

Items for reporting	Report to BH HREC (when BH HREC is the reviewing HREC)	Report to BH RGO (when the reviewing HREC is external, not BH HREC)	Other Reporting Requirements
Annual Safety Report from Sponsor or DSMB	Sponsor to Report to BH HREC annually along with Progress Report	Sponsor to Report to BH RGO annually along with Progress Report (include central HREC approval)	Provided by Sponsor
Individual USADE **Further advice and forms can be found here**	Report to HREC **within 72 hours**	Report to RGO **within 72 hours** if USADE occurs locally	Report to Sponsor
Individual SUSARs	Report to HREC **ONLY** if the PI/DSMB determines there is local site impact	Report to RGO **ONLY** if the PI/DSMB determines there is local site impact	Always report to Sponsor **without undue delay**
Significant Safety Issue (SSI)	Notify HREC **within 72 hours** if USM otherwise within 15 calendar days (see Table 1)	Notify RGO **within 72 hours** if USM otherwise within 15 calendar days (see Table 1)	Report to Sponsor **within 72 hours**
Urgent Safety Measure (USM)	Notify HREC **within 72 hours**	Notify RGO **within 72 hours**	Report to DSMB/Sponsor **within 72 hours**
IB/Product Information Update	Please submit to the HREC and include: - Amendment Form - Full revised IB - Summary of changes	Report to RGO ONLY if PI determines there is local site impact (include central HREC approval)	Provided by Sponsor
Non serious breach/Protocol Deviations	Report to the HREC when the Sponsor/PI/DSMB determines there is local site impact	Report to the RGO ONLY if the Sponsor/PI/DSMB determines there is local site impact	Report all to Sponsor
Serious Breach	Submit to HREC **within 72 hours of confirmation of serious breach by sponsor**	Submit to RGO; **within 72 hours if occurring at Barwon Health,** otherwise within 7 calendar days	Completed by Sponsor
Suspected Breach	Submit to HREC **within 72 hours of confirmation of serious breach by sponsor**	Submit to RGO; **within 72 hours of confirmation of serious breach by sponsor if occurring at Barwon Health,** otherwise within 7 calendar days	Report to sponsor **within 72 hours**
Suspected Breach (Third Party – PI and/or Institution)	Report directly to HREC **within 7 calendar days**	Report directly to RGO **within 7 calendar days**	HREC will report to sponsor

Please Note: Excepting annual safety reports, interim DSUR and DSMB reports should only be reported to HREC/RGO when there is site impact.

Any other event not covered in the above table which materially impacts the continued ethical acceptability of the research, and/or if action is planned, must be reported to the Sponsor, HREC and/or RGO in a prompt manner.

All items must be submitted to REGI@barwonhealth.org.au using the REGI email submission template and the relevant and most recent Department of Health & Human Services' (DHHS) forms.

Forms and templates can be found on the REGI Unit's webpage by clicking here. To access the DHHS's forms directly, please click here.

Principal Investigator Responsibilities when Barwon Health is the Sponsor

Where Barwon Health is the Sponsor of an Investigator Initiated Project, please refer to Table 3 and Table 4 for Principal Investigator Responsibilities.

Table 3: Safety reporting requirements for Barwon Health Principal Investigators when Barwon Health is Sponsor

Item	When the reviewing HREC is BH HREC	When the reviewing HREC is external report to BH RGO	Other PI Reporting Requirements
Annual Safety Report from Sponsor/DSMB	Report to BH HREC annually along with Progress Report and include: - Sponsor and PI comments as to whether action is planned for the trial on the basis of the reports	Report to BH RGO annually along with Progress Report (including central HREC approval) and include: - Sponsor and PI comments as to whether action is planned for the trial on the basis of the reports	Provided by DSMB annually or as necessary (please have your DSMB complete a 'BH Annual Safety Report' form)
Individual SAEs	Report to BH HREC ONLY if DSMB/Sponsor/PI determines there is impact	Report to RGO ONLY if DSMB/Sponsor/PI determines there is impact	Report to DSMB
Individual USADE **Further advice and forms can be found here**	Report to HREC **within 72 hours**	Report to RGO **within 72 hours** if USADE occurs locally	Report to TGA, DSMB and all Investigators within 7 calendar days (fatal/life threatening) otherwise no later than 15 calendar days
Individual SUSARs	Report to HREC **ONLY** if the PI/DSMB determines there is local site impact	Report to RGO **ONLY** if the PI/DSMB determines there is local site impact	Report to TGA, DSMB and all Investigators **without undue delay**
Significant Safety Issue (SSI)	Notify HREC **within 72 hours** if USM otherwise within 15 calendar days (see Table 1)	Notify RGO **within 72 hours** if USM otherwise within 15 calendar days (see Table 1)	Report to TGA, DSMB and all Investigators **without undue delay**
Urgent Safety Measure (USM)	Notify HREC **within 72 hours**	Notify RGO **within 72 hours**	Report to TGA, DSMB and all Investigators **within 24 hours**
IB/Product Information Update	Please submit to the HREC Include: - Amendment Form - Full revised IB - Summary of changes	Report to RGO (include central HREC approval of IB update)	Updates are provided by drug/device supplier (PI to determine if protocol and PICF need amendment)
Non serious breach/Protocol Deviation	Report to the HREC when the PI/DSMB determines there is local site impact	Report to the RGO when the PI/DSMB determines there is local site impact	Report to DSMB
Serious Breach	Submit to HREC **within 72 hours**	Submit to RGO **within 72 hours**	Report to DSMB/REGI **within 72 hours**
Suspected Breach	Report directly to HREC **within 72 hours of confirmation by DSMB of serious breach**	Report directly to RGO **within 72 hours of confirmation by DSMB of serious breach**	Notify DSMB/REGI **within 72 hours**

Any other event not covered in the above table which materially impacts the continued ethical acceptability of the research, and/or if action is planned, must be reported to the Sponsor, HREC and/or RGO in a prompt manner.

All items must be submitted to REGI@barwonhealth.org.au using the REGI email submission template and the relevant and most recent Department of Health & Human Services' (DHHS) forms.

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Significant Safety Issues

A safety issue that could adversely affect the safety of participants or materially impact on the continued ethical acceptability or conduct of the trial (can include USM).

SSIs do not fall within the definition of a SUSAR and often require other action.

Examples of SSIs:

- An SAE associated with trial procedures and that requires modification of the conduct of a trial
- A major safety finding from a newly completed animal study
- Recommendations from DSMB e.g. an increase in frequency or severity of expected AR
- Single case events that lead to an USM

The below table lists actions to be taken for types of SSIs and how to report on these actions.

Table 4: Sponsor Reporting of **Significant Safety Issues**

ACTION	What is communicated	Recipients	Timelines and further review
Urgent Safety Measure	- Reasons for the urgent safety measure - Measures taken - Further actions required	Notify TGA, DSMB, Investigators and reviewing HRECs and all site RGOs	No later than **72 hours** of the measure being taken HRECs are not required to approve USMs, but may consider if proposed actions are appropriate
Notification of an Amendment	- Details of the significant safety issue - Further actions planned	Notify TGA, DSMB, Investigators and reviewing HRECs and all site RGOs	No later than **15 calendar days** of becoming aware HREC amendment must be submitted **without undue delay**
Temporary Halt of a Trial for Safety Reasons	- Reasons for the halt - The scope of the halt - Measures taken - Further actions required	Notify TGA, DSMB, Investigators and reviewing HRECs and all site RGOs	No later than **15 calendar days** from halt Letter to HREC describing actions taken no later than **15 calendar days** from halt
Early Termination of a Trial for Safety Reasons	- Reasons for the early termination - Measures taken - Further actions planned	Notify TGA, DSMB, Investigators and reviewing HRECs and all site RGOs	No later than **15 calendar days** from early termination Letter to HREC describing actions taken no later than **15 calendar days** from early termination

References

- NHMRC (2016) Safety monitoring and reporting in clinical trials involving therapeutic goods
- NHMRC (2018) Data Safety Monitoring Boards (DSMBs)
- NHMRC (2018), Reporting of Serious Breaches of Good Clinical Practice (GCP) or the Protocol for Trials Involving Therapeutic Goods