Purpose

To explain the Investigator reporting requirements to Bellberry HREC in the event of a serious breach, protocol violation or protocol deviation as per 'Reporting of Serious Breaches of Good Clinical Practice (GCP) or the Protocol for Trials Involving Therapeutic Goods' guidelines of the National Health and Medical Research Council (NHMRC).

Definitions

Serious breach: is a breach of Good Clinical Practice or the protocol that is likely to affect to a significant degree the safety or rights of a research participant or the reliability and robustness of the data generated in the research project. Sponsors have primary responsibility for determining whether any suspected breach meets the definition of a serious breach. Examples may include (*Please see Appendix 1 for further examples of serious breaches from the NHMRC)*:

- Failure to appropriately obtain informed consent, i.e., there is no documentation of informed consent or informed consent was obtained after initiation of study procedures.
- Enrolment of a participant who did not meet all inclusion/exclusion criteria.
- Performing a study procedure not approved by the HREC.
- Failure to report a serious adverse event to the HREC and/or sponsor.
- Failure to perform a required laboratory test that, in the opinion of the PI, may affect participant safety or data integrity.
- Drug/study medication dispensing or dosing error.
- Study visit conducted outside of required timeframe that, in the opinion of the PI, may affect participant safety or data integrity.
- Failure to follow safety monitoring plan.
- Breach of participant confidentiality (by site or sponsor).

Non-compliance: failure to comply with National regulations, State laws, Institutional policies, requirements or determinations of the HREC, and/or provisions of the approved research study. Non-compliance may also occur when there is a need to deviate from the approved protocol in order to protect the welfare of research participants.

Serious non-compliance: failure to comply with National regulations, State laws, Institutional policies, requirements or determinations of the HREC, and/or provisions of the approved research study, where the occurrence involves substantive potential or actual increased risk to the safety, rights and welfare of research participants.

Continuing non-compliance: is repeated occurrences of non-compliance by the same investigator or by the Institution. Repetition may be of the same occurrence or different occurrences. This repetition may be in the same or in different protocols by a single investigator. Such repetition if unaddressed may affect the protection of human research participants. For the institution, repetition may be of the same or different policies, procedures, regulations and/or laws.

Protocol deviation: is a less serious form of non-compliance, usually arising in dealing with unforeseen circumstances and can be agreed between the sponsor and the investigator either in advance or after the event. Protocol deviations may be considered slightly differently to protocol violations in that they generally do not have a major impact on participant welfare or data integrity. Examples of a protocol deviation may include the scheduling of a required procedure outside the time frame specified in the protocol or the use of a prohibited concomitant medication by a participant. Deviations are not required to be reported to Bellberry.

Protocol violation: a divergence from the protocol that materially (a) reduces the quality or completeness of the data, (b) makes the Participant Information and Consent Form inaccurate, or (c) impacts on a participant's safety, rights, or welfare. The Bellberry HREC does not require notification of a protocol violation.

Third Parties: some serious breaches may be identified by third parties (e.g. trial sites) who wish to report directly to the reviewing HREC. This would usually be appropriate if:

- The investigator/institution has good evidence that a serious breach has occurred, but the sponsor disagrees with their assessment and is unwilling to notify the HREC.
- The investigator/institution has become aware that the sponsor may have committed a serious breach.

Guidance

Reporting timeframe

Report serious breaches to the reviewing HREC within 7 calendar days of confirming a serious breach has occurred and provide follow-up reports when required. These should be reported utilising the 'Start Protocol Violation Report Form' in eProtocol.

All serious breaches must be submitted to the HREC after completing the NHMRC sponsor or third-party serious breach report templates (see references) and other documentation, for example the CAPA.

Reporting of serious breaches by the sponsor

Sponsors have primary responsibility for determining whether any suspected breach meets the definition of a serious breach. In practice, this assessment is often conducted or overseen by the group tasked with monitoring the general quality of the trial and its adherence to the protocol. Sponsors should also:

- Develop documented processes for managing serious breaches including:
  - The assessment of whether the serious breach is isolated or systemic
  - The assessment of the impact of the serious breach on participants and on the reliability and integrity of trial data
  - The investigation procedure
  - The reporting procedure
  - The management of corrective and preventative action (CAPA)
  - The circulation and retention of documents relating to serious breaches.
- For serious breaches occurring at a trial site, notify the site's principal investigator within seven calendar days of confirming a serious breach has occurred.
- Perform a root cause analysis and ensure that appropriate corrective and preventative actions are taken.
- Where the sponsor determines a third-party report, provided to it by the HREC, meets the definition of a serious breach, report the serious breach to the reviewing HREC within seven calendar days of this decision.
- Where the sponsor determines a third-party report, provided to it by the HREC, does not meet the definition of a serious breach, notify the reviewing HREC by letter or e-mail, including a justification for this decision, within 7 calendar days of confirming a serious breach has not occurred.
- Keep written records of all suspected and confirmed serious breaches, including the justification for determining that a suspected breach does not meet the definition of a serious breach.
- Notify the TGA and the reviewing HREC if the serious breach leads to the closure of the site.
- Report to the TGA any serious breach that involves a defective product that may have wider implications for the supply chain for that marketed product:
  - Commercial sponsors report to the TGA using existing product surveillance processes

- Non-commercial sponsors (e.g. universities) may either report to the TGA directly or to the Marketing Authorisation Holder/manufacturer (who would report to the TGA).

Reporting of serious breaches by third parties

The majority of suspected breaches will be identified by the sponsor either through routine monitoring or through direct reporting of deviations from trial sites. Sponsors may also identify serious breaches that have occurred as a result of a failure of their own quality systems, which they should report in the same manner. However, some serious breaches may be identified by third parties (e.g. trial sites) who wish to report directly to the reviewing HREC.

Responsibility of the HREC and potential HREC actions

The Chair of the HREC will take whatever actions are deemed necessary to address the unanticipated problem(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 participants of new information,
- require modifications to the informed consent,
- require modifications to the protocol when permissible,
- require the investigator to re-consent enrolled participants,
- increase monitoring of participants,
- increase frequency of continuing review,
- observation or monitoring of the research,
- require additional training and education,
- referral to other organisational entities.

After the HREC Chair/and delegates have received all required documentation to complete their review, a determination will be communicated to the investigator via eProtocol within a reasonable timeframe, but no later than ten business days of the HREC's decision.

When the HREC determines that an unanticipated problem 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

NHMRC Guidance on reporting serious breaches of GCP

National Statement on Ethical Conduct in Human Research (2023)

MAR F3.1.1 Serious breaches report form – sponsor

MAR F3.1.2 Serious breaches report form – third party

Appendix 1: Examples of Serious Breaches

The table below is from '*Reporting of Serious Breaches of Good Clinical Practice (GCP) or the Protocol for Trials Involving Therapeutic Goods'* guidelines of the National Health and Medical Research Council (NHMRC).

The following table provides some examples of the assessment of serious breaches. This list is not exhaustive and other types of serious breaches may occur.

Dosing errors reported: 1) A participant was dosed with the incorrect IMP which was administered via the incorrect route (the IMP used was from a completely different clinical trial to the one the participant was recruited to).	**Yes**, there was potential for significant impact on the safety or rights of trial participants.
2) A participant was dosed with the IMP from the incorrect treatment arm. In addition, some months later, the participants in an entire cohort were incorrectly dosed with IMP three times daily when they should have been dosed once daily.	**Yes**, there was significant impact on the safety or rights of trial participants and on data reliability/ robustness. In addition, the issue was systematic and persistent and continued despite implementation of a corrective and preventative action plan.
3) One participant was administered six additional doses of the IMP. The participant was to receive the IMP on day 1 *and* 8 but instead received the IMP on days 1 *to* 8. The participant experienced a severe adverse event as a result.	**Yes**, there was significant impact on the safety or rights of the trial participant
4) IMP had expired and was awaiting relabelling for extension of the use by date, which had been approved by the sponsor's Authorised Person. 9 The IMP had not been quarantined as requested and had been dispensed to one patient shortly after the expiry.	**No**, because there was no impact on the safety or rights of the trial participant as the label extension had been approved. If this were to happen more than once, it might then become a serious breach.
5) IMP temperature excursions reported.	**Yes**, if the excursion was not managed and participants were dosed with the IMP assessed as unstable. **No**, if the excursions had been managed appropriately (e.g., the IMP was moved to an alternative location/quarantined as necessary and an assessment confirmed that there was no impact on participant safety or data integrity).
6) Blood samples from a cohort were invalid due to being processed incorrectly. As a result, one of the secondary endpoints could not be met.	**Yes**, exclusion of the data from the analysis impacted data reliability/robustness.
7) Multiple issues with the Interactive Response Technology (IRT) system across several clinical trials leading to the dispensing of expired IMP and a shortage of IMP at investigator sites.	**Yes**, the issue was persistent and there was significant impact on the safety or rights of trial participants and data reliability/robustness.
8) Repeat ECGs were not performed, as required by the protocol. There was inadequate quality control of the interim safety reports used for dose escalation, which gave rise to the potential for stopping criteria to be missed.	**Yes**, there was potential for significant impact on the safety or rights of trial participants.

9) The investigator failed to report one SAE as defined in the protocol in a trial where the safety profile of the IMP was well characterised (re-training provided).	**No**, as there was no significant impact on the safety or rights of the participant.
10) Investigator site failed to reduce or stop trial medication in response to certain laboratory parameters, as required by the protocol. Participants were exposed to an increased risk of thrombosis. This occurred with several participants over a one-year period, despite identification by the monitor of the first two occasions.	**Yes**, there was potential for significant impact on the safety or rights of trial participants.
11) On three occasions a site failed to see a patient within the protocol-specified visit window.	**No**, the deviation had minimal impact on participant safety or data reliability/robustness. The deviations were a consequence of unnecessarily narrow inclusion criteria, which was rectified through a protocol amendment.
12) Participant Information Sheet and Consent Form was updated with significant new safety data (a new drug-drug interaction). At one trial site, this was not relayed to the participants until approximately 3 months after approval.	**Yes**, the failure to inform participants in a timely manner resulted in significant impact on their safety or rights.
13) Poor communication/protocol instructions from a sponsor to the site in a chemotherapy trial resulted in the wrong equipment being used to dose the participant (an infusion pump instead of a syringe driver). Participants were significantly under-dosed.	**Yes**, there was significant impact on the safety of trial participants and the reliability /robustness of trial data.