

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:

- 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 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 \(2007 incorporating all updates\)](#)

MAR F3.1.1 Serious breaches report form – sponsor

MAR F3.1.2 Serious breaches report form – third party