Australian Government
National Health and Medical Research Council

NHMRC

Reporting of Serious Breaches of Good Clinical Practice (GCP) or the Protocol for Trials Involving Therapeutic Goods

2018

WORKING TO BUILD A HEALTHY AUSTRALIA

Publication Details

Publication title:	Reporting of Serious Breaches of Good Clinical Practice (GCP) or the Protocol for Trials Involving Therapeutic Goods
Published:	2018
Publisher:	National Health and Medical Research Council
NHMRC Publication reference:	EH59A
Online version:	www.nhmrc.gov.au/guidelines-publications/EH59A
ISBN Online:	978-1-86496-001-3
Suggested citation:	National Health and Medical Research Council (2018), Reporting of Serious Breaches of Good Clincal Practice (GCP) or the Protocol for Trials Involving Therapeutic Goods

Contact us

To obtain information regarding NHMRC publications or submit a copyright request, contact:

E: nhmrc.publications@nhmrc.gov.au

P: (02) 6217 9000

Contents

Guidance on the Reporting of Serious Breaches

1. Background

A need for supplementary guidance to establish a reporting framework for **protocol deviations**[1] was identified following a revision of the AHEC Position Statement on *Monitoring and Reporting of Safety for Clinical Trials Involving Therapeutic Goods (May 2009)*, which was re-published by the NHMRC in November 2016 as *Guidance on Safety Monitoring and Reporting in Clinical Trials Involving Therapeutic Goods*.[2]

This guidance brings together advice from regulatory authorities, clinical trial groups, and industry organisations on the reporting of deviations from Good Clinical Practice (GCP) or the protocol.

2. Introduction and scope

Deviations from GCP or the protocol should lead to 'prompt action by the sponsor to secure compliance'.[3] GCP requires all deviations to be reported to, and collated by the sponsor so that corrective and preventative action can be implemented and so that their impact on the analysis of the data can be considered when the clinical study report is produced. The European Union's (EU) *Clinical Trials Regulation* (536) introduced the term **serious breach** to describe the sub-set of deviations that should be reported to review bodies and the Integrated Addendum to ICH E6 R1: *Guidelines for Good Clinical Practice (ICH E6 R2)* requires the sponsor to perform a root cause analysis for *'noncompliance* [deviations] *that significantly affects or has the potential to significantly affect human subject protection or reliability of trial results'*.

This guidance sets out a framework for the management and reporting of serious breaches. Its purpose is to:

- clarify GCP Guideline requirements for reporting deviations
- rationalise the reporting of protocol deviations to align with GCP, which only requires the reporting of a small sub-set of deviations to review bodies
- adopt a standard term ('serious breach') to describe this sub-set
- clarify the roles of key stakeholders
- define standard reporting timelines
- provide standard forms for serious breach and suspected breach reporting to Human Research Ethics Committees (HRECs) to replace the forms currently used within jurisdictions to report protocol deviations (Appendix I and II).

1 To avoid confusion over terminology, the term *'deviation'* (recommended by ICH E3 – *Structure and Content of the Clinical Study Report* 2012) has been used to descibe any breach, divergence or departure from the requirements of Good Clinical Practice or the clinical trial protocol, whether minor or major. Although the term 'violation' is also widely used in place of 'deviation' or to represent a subset of deviations, it is not recommended by ICH (E3).

2 https://www.nhmrc.gov.au/guidelines-publications/eh59

3 Integrated Addendum to ICH E6 R1: *Guidelines for Good Clinical Practice (ICH E6 R2)*: Section 5.20.1

Although GCP requires all deviations to be reported to the trial sponsor, not all deviations require reporting to review bodies. HRECs need only 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 (hereinafter referred to as **serious breaches**).[4] 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.

This guidance applies to both commercial and non-commercial clinical trials involving therapeutic goods.

3. Definitions

Term	Definition
Audit	A systematic and independent examination of trial related activities and documents to determine whether the evaluated trial related activities were conducted, and the data were recorded, analysed and accurately reported according to the protocol, sponsor's standard operating procedures (SOPs), Good Clinical Practice (GCP), and the applicable regulatory requirement(s).
Clinical Trial	Any research study that prospectively assigns human participants or groups of humans to one or more health-related interventions to evaluate the effects on health outcomes.
Commercial Trial	A trial that is funded and sponsored by a commercial company, where the company designs the protocol and owns the results and intellectual property rights arising from the trial.
Coordinating Principal Investigator (CPI)	a) In relation to a clinical trial conducted at a single trial site, the principal investigator at that site b) In relation to a clinical trial conducted at more than one trial site, the health professional, whether or not he or she is an investigator at any particular site, who takes primary responsibility for the conduct of the trial.
Deviation	Any breach, divergence or departure from the requirements of Good Clinical Practice or the clinical trial protocol.
Principal Investigator (PI)	The person responsible, individually or as a leader of the research team at a site, for the conduct of a trial at that site. In a single centre trial, the principal investigator may also be the coordinating principal investigator.
Non-Commercial Trial	A trial where a non-commercial (not for profit) organisation retains control of the protocol and is the trial sponsor. Non-commercial trials are usually publically funded (e.g. by government/charities), but may also be funded/supported by a commercial company.
Serious Breach	A breach of Good Clinical Practice or the protocol that is likely to affect to a significant degree: a) The safety or rights of a trial participant, or b) The reliability and robustness of the data generated in the clinical trial. Note: this guidance's definition of **serious breach** differs from the definition in the *Australian Code for the Responsible Conduct of Research* and is about deviations from the requirements of Good Clinical Practice or the clinical trials protocol.
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.
Sponsor	An individual, organisation or group taking on responsibility for securing the arrangements to initiate, manage and finance a study.
Suspected Breach	A report that is judged by the reporter as a possible serious breach but has yet to be formally confirmed as a serious breach by the sponsor.

4 Risk-averse over-reporting is discouraged. It is anticipated that, if the definition is applied correctly, the numbers of reported cases would be significantly less than the number of protocol deviations currently reported to HRECs.

Term	Definition
Third Party	Any entity (other than the trial sponsor) wishing to report a suspected breach.
Urgent Safety Measure	A measure required to be taken in order to eliminate an immediate hazard to a participant's health or safety. *Note: An urgent safety measure can be instigated by either the investigator or sponsor and can be implemented before seeking approval from HRECs or institutions.*

4. 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. In particular, the judgement on whether a breach is likely to have a significant impact on the reliability and robustness of trial data should be made by the sponsor and depends on a variety of factors; for example, the design of the trial, the type and extent of the data affected by the breach, the overall contribution of the data to key analysis parameters, and the impact of excluding the data from the analysis. However, 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.

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 robustness 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.
- Report[5] serious breaches to the reviewing HREC within **7 calendar days** of confirming a serious breach has occurred and provide follow-up reports when required.
- For serious breaches occurring at a trial site,[6] notify the site's principal investigator within **7 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,[7] provided to it by the HREC, meets the definition of a serious breach, report the serious breach to the reviewing HREC within **7 calendar days** of this decision.

5 See Appendix I (Serious Breach Report Form - Sponsor). The sponsor or their delegate should report serious breaches directly to the reviewing HREC.

6 Investigators and their institutions only receive serious breach reports that have occurred at their site. If a serious breach impacts all sites, the actions arising will be communicated to sites (e.g. a product recall resulting from a breach relating to the manufacture of IMP).

7 See Section 5 and Appendix II (Suspected Breach Report Form - Third Party).

- 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[8] 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).

Note: The sponsor may be required to demonstrate (e.g. during an audit) its adherence to reporting timeframes and also the timeliness of its processes for assessing serious breaches. However, it is expected that, for certain suspected breaches, some degree of investigation and assessment may be required prior to notification in order to confirm that a serious breach has actually occurred.

It is recommended that sponsors also ensure that agreements with trial sites and other vendors include a reference to a reporting timeline of **72 hours** for notifying the sponsor of any suspected breach.

5. 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. 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.

6. Responsibilities of other entities

a) The Therapeutic Goods Administration (TGA)

The role of the TGA is to act on notifications of any important defects relating to therapeutic goods supplied to the Australian market by assessing their impact on marketed products.

The TGA has the authority to inquire into and investigate non-compliance with GCP standards for clinical trials under the CTN and CTX scheme. The TGA may also inspect clinical trials sites under the CTX scheme.

8 For trials conducted under the Clinical Trial Exemption/Clinical Trial Notification Scheme (CTX/CTN Scheme) only.

b) The reviewing HREC

The role of an HREC in reviewing serious breaches is to evaluate the impact of the serious breach on the continued ethical acceptability of the study and to satisfy itself that the the serious breach is managed appropriately; for example, through an amendment to trial documentation. Serious breaches may raise issues on which ethical advice is required; for example, whether participants should be reconsented if a report of a serious breach has identified inadequacies in the consent process. HRECs may also assess whether any corrective and/or preventative actions implemented or planned are appropriate and have adequately addressed the underlying issue.

Where the sponsor has notified the HREC of the serious breach, the HREC should:

- Assess the report, including any corrective and preventative actions implemented, and provide any necessary feedback to the sponsor.
- For trials conducted under the CTX/CTN Scheme, inform the TGA and the sponsor if the notification of a serious breach leads to the suspension or withdrawal of the ethics approval for the trial.

Where a third party has notified the HREC of a suspected breach, the HREC should:

- Inform the sponsor of the suspected breach report.
- If the sponsor confirms to the HREC that a serious breach has not occurred,[9] but the rationale for not reporting the serious breach is unclear or contested by the HREC, request a written justification or explanation from the sponsor.
- For trials conducted under the CTX/CTN Scheme, inform the TGA and the sponsor if the notification of a serious breach leads to the suspension or withdrawal of the ethical approval for the trial.

c) The principal investigator

The principal investigator should:

- Ensure that the trial team is aware of the process for reporting serious breaches.
- Report any suspected breaches to the sponsor **within 72 hours** of becoming aware of the suspected breach.
  Note: Exceptionally, the investigator, in liaison with their institution, may report the suspected breach directly to the HREC (see Section 5).
- Report all serious breaches that have been confirmed by the sponsor as occurring at the site to their institution (research governance office) **within 72 hours** of being notified of the serious breach.
- Provide any follow-up information as required.
- Work with the institution or sponsor, as appropriate, to implement any corrective and preventative actions that may be indicated.

9 This confirmation may be communicated to the HREC by letter or e-mail

d) The institution where the trial is being conducted

The institution should:

- Develop clear guidance for investigators detailing the reporting and management of serious breaches that is consistent with the framework set out in this document.
- Assess each serious breach to determine its impact, e.g. any impact on other trials conducted by the institution/investigator.
- Facilitate the implementation of any corrective and preventive actions if required by the sponsor.
- Take advice from the reviewing HREC regarding its assessment of the breach.
- Inform the HREC if a serious breach leads to withdrawal of the site's authorisation.
- Consider whether the conduct determined to be a serious breach requires the application of the *Australian Code for the Responsible Conduct of Research*.

Appendix I: Serious Breach Report Form (Sponsor)

SERIOUS BREACH REPORT FORM (SPONSOR)			
This form should be completed when the trial sponsor is reporting a serious breach to the Human Research Ethics Committee (HREC) or when a sponsor is providing additional/follow-up information following a third party report of a confirmed serious breach			
HREC reference number:		Date of this report:	
Project title:			
HREC:		Coordinating Principal Investigator	
Sponsor:		Sponsor Contact (Aus):	
Initial Report: ☑ Follow-up Report: ☑			
Details of the organisation/individual committing the serious breach:			
Details of the serious breach			
Indicate the impact of the serious breach on any of the following:			
Participant safety:		Reliability and robustness of data:	
Participant rights:			
Provide: 1) An explanation of where, how and when the serious breach occurred and how it was identified 2) Any other relevant information (e.g. project status)			
Details of any action taken to date*			
Include: 1) Any investigations you/others are conducting 2) The outcome of those investigations if completed (or details of when they will be available/reported) 3) How the serious breach will be reported in the final report/publication 4) Any corrective and preventative action implemented to ensure the serious breach does not occur again *If the investigation or the corrective/preventative action is ongoing at the time of this report, please indicate your plans with projected timelines for completion and provide any further information in a follow-up report.			

Appendix II: Suspected Breach Report Form (Third Party)

SUSPECTED BREACH REPORT FORM (THIRD PARTY)			
This form should be completed when a third party (e.g. individual/institution) wishes to report a suspected breach of Good Clinical Practice or the protocol directly to the reviewing HREC without reporting through the sponsor			
Please provide the following details (if known):			
HREC reference number:		Date of this report:	
Project title:			
HREC:		Coordinating Principal Investigator:	
Reporter name:			
Organisation:			
Contact details:			
Role in/connection to the project:			
Details of the organisation/individual committing the suspected breach:			
Details of the suspected breach			
Provide 1) An explanation of where, how and when the suspected breach was identified 2) Any other relevant information			

Appendix III: Serious Breach: Questions and Answers

1. Should serial deviations/breaches (i.e. numerous or persistent minor deviations/breaches) be reported as a serious breach of the requirements of Good Clinical Practice or the protocol?

Maybe. Serial deviations/breaches may be indicative of a general failure in a quality system. When considered collectively, such serial deviations/breaches may impact on the safety/rights of participants or the reliability/robustness of data generated in the trial and result in the requirement to report a serious breach. For example, widespread and uncontrolled use of protocol waivers affecting eligibility criteria may lead to a serious breach report.

Note: this guidance's definition of **serious breach** differs from the definition in the *Australian Code for the Responsible Conduct of Research* (the Code) and repeated or persistent breaches of Good Clinical Practice or the protocol may also constitute a breach of the Code.

2. How does a serious breach differ from a significant safety issue (SSI)?

The definitions *significant safety issue* and serious breach are similar (Section 3); however, they differ by virtue of the fact that a serious breach only results from a deviation of the protocol or GCP whereas a SSI may arise in a trial without any such deviation occurring. In addition, the serious breach reporting system enables the escalation of issues concerning both participant safety and data reliability.

3. Should an event leading to the death, hospitalisation or permanent disability of a trial participant in Australia be reported as a serious breach?

Safety reports such as a Suspected Unexpected Serious Adverse Event (SUSAR), an Unanticipated Serious Adverse Device Effect (USADE) or a significant safety issue (SSI) occurring in Australia usually do not meet the definition of a serious breach. However, these types of safety report may result from an underlying serious breach and, in these instances, the underlying serious breach should be reported. The reporting of the serious breach does not remove the requirement for the SUSAR/USADE or SSI to be reported, in accordance with Australian guidance.

4. For trials that are conducted in Australia, should serious breaches that occur at non-Australian sites be reported?

No. But if the non-Australian serious breach is identified as having significant impact on the safety or rights of Australian participants or the reliability or robustness of the data generated in the trial, other types of report may be applicable, e.g. the report of a significant safety issue.

5. Can a sponsor prospectively approve deviations (protocol waivers) without or before HREC approval?

NHMRC has aligned their advice on protocol waivers with the European Medicines Agency.

As adherence to the protocol is a fundamental part of the conduct of a clinical trial, sponsors and investigators should not use systems of prospectively approving protocol deviations, in order to effectively widen the scope of a protocol. Protocol design should be appropriate to the populations required and if the protocol design is defective (i.e. resulting in the need for serial protocol waivers), a protocol amendment should be submitted to the HREC.

Note: GCP Guidelines do permit deviations, without prior HREC approval, when they are necessary to eliminate an immediate hazard to a trial participant's health or safety (i.e. an urgent safety measure).

GCP Guidelines also permit deviations by the sponsor, without HREC approval, that involve only logistical or administrative aspects of the trial (e.g., change of monitor(s), telephone number(s)).

6. Should a failure to report adverse events be reported as a serious breach?

Maybe. When there is significant potential for impact on participant safety when adverse events are not reported in accordance with the protocol, a serious breach should be reported. For example, inadequate safety reporting in a dose escalation study may result in an inappropriate dose escalation decision that may impact on participant safety. However, each case should be assessed for impact and not all instances would result in a serious breach report (see example (9) Appendix IV).

7. Does confirmation of scientific misconduct meet the definition of a serious breach?

The reporting of scientific misconduct is outside the scope of this guidance. Please refer to the *Australian Code for the Responsible Conduct of Research* (the Code) for further guidance.

Appendix IV: Examples of Serious Breaches

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.

Details of the report	Was a serious breach confirmed?
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 As defined in the PIC/S Guide to Good Manufacturing Practice for Medicinal Products.

Details of the report	Was a serious breach confirmed?
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.

Acknowledgement and References

With kind permission, this guidance has been adapted from the guidance produced by the Medicines and Healthcare Products Regulatory Authority (MHRA).

References

- Integrated Addendum to ICH E6 (R1): *Guidelines for Good Clinical Practice.*
- ISO 14155 (2011) - *Clinical Investigation of Medical Devices for Human Subjects – Good Clinical Practice.*
- *Guidance for the notification of serious breaches of GCP or the Trial Protocol*: Medicines and Healthcare Products Regulatory Authority (MHRA).
- Regulation (EU) No 536/2014 of the European Parliament and of the council of 16 April 2014 on *clinical trials on medicinal products for human use,* and repealing Directive 2001/20/EC.
- *Access to Unapproved Therapeutic Goods* - Clinical Trials in Australia.
- *The Australian Code for the Responsible Conduct of Research* 2007.

Working Party

Working Party:

Professor Ingrid Winship	Executive Director of Research for Melbourne Health and AHEC Member
Adjunct Professor Nikolajs Zeps	Director of Research at SJGHC Subiaco Hospital
Melissa Hagan	Manager, Health and Medical Research at Queensland Health
Professor James Toouli	Emeritus Professor of Surgery at Flinders University Adelaide
Mounir Mina	Therapeutic Goods Administration (TGA)
Dr Wendy Hague	Clinical Trials Program Director, NHMRC Clinical Trials Centre
Val Theisz	Medical Technology Association of Australia (MTAA)
Tanya Symons	Consultant Technical Writer