Title: Standard Operating Procedure (SOP) | MCRI Sponsor-Investigator Management of Non-Compliance: Protocol Deviations and Serious Breaches

Document ID: MCTC123
Version: 1.0
Applicability: Central Managing Team, MCRI-sponsored investigator-initiated trials

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24-Mar-2022 @ 11:28 AM AEDT Reason: Approval

This document is effective from the date of the last approval signature and will be reviewed in two years.

Document History

Revision	Modified by	Change No.	Description of Change
1.0	N/A	N/A	New Issue

Contents

1. PURPOSE

Clinical trials should be managed and conducted in accordance with the approved protocol, Sponsor and Site Standard Operating Procedures (SOPs), Good Clinical Practice (GCP) and relevant regulations.

Sponsors and Principal Investigators have responsibilities for managing non-compliance with GCP, the protocol and trial-related SOPs in accordance with:

- NHMRC: Reporting of Serious Breaches of Good Clinical Practice (GCP) or the Protocol for Trials Involving Therapeutic Goods
- TGA: Guideline for Good Clinical Practice [with TGA annotations]

For investigator-initiated trials sponsored by MCRI, MCRI delegates the Sponsor responsibility for managing and reporting non-compliance to the MCRI Sponsor-Investigator.

For non-commercial trials sponsored by a collaborative research group, the Coordinating Principal Investigator (CPI) will be responsible for managing and reporting non-compliance. This responsibility is outside the scope of this SOP.

This SOP describes the procedures for the MCRI Sponsor-Investigator to manage and report non-compliance, including serious breaches to the reviewing HREC, Therapeutic Goods Administration (TGA) and Site Principal Investigator(s).

2. BACKGROUND

Deviations from GCP or the protocol should lead to prompt action by the Sponsor to secure compliance. GCP requires all deviations to be reported to and collated by the Sponsor so that the impact on participant safety and data can be determined and a Corrective and Preventive Action plan (CAPA) can be implemented, if required. Non-compliance with the protocol or GCP can lead to:

- Reduced integrity of the trial data, as the reliability and robustness of the clinical trial data is affected.
- Compromised participant safety; and
- Nullification of a trial's insurance/indemnity.

All non-compliance with the protocol and GCP must be reported to the Sponsor. Importantly, expedited reporting is only required for a subset of non-compliance that is likely to affect to a significant degree either the safety or rights of a trial participant or the reliability and robustness of the trial data. The term used for this subset is a serious breach.

All serious breaches must be reported to both the Sponsor and reviewing HREC. All other non-compliance is captured via the participant Case Report Form (CRF) and the Site Non-Compliance log. Refer to Section 4 for the process for recording and reporting all events of non-compliance.

Refer to Appendix 3 for detailed examples of non-compliance and guidance for when to consider the non-compliance a serious breach.

3. RESPONSIBILITY AND SCOPE

This SOP applies to staff involved in conducting trials at MCRI at the Sponsor level: Sponsor-Investigators, and members of the central coordinating trial team who are responsible for liaising with staff at participating sites, e.g. Trial Coordinator.

For MCRI-sponsored investigator-initiated trials where MCRI/RCH is participating as a Site, the MCRI-Sponsor-Investigator is the Site PI and as such is responsible for implementing the procedures set out in this SOP in addition to those outlined in SOP MCRI/RCH Site Principal Investigator Management of Non-Compliance: Protocol Deviations and Serious Breaches [MCTC112].

Sponsor responsibilities of MCRI Sponsor-Investigators include:

1. Providing site teams with a process for reporting protocol deviations and suspected serious breaches, i.e. provide a trial-specific non-compliance report form and instructions for recording these events in the CRF.
2. Reviewing suspected serious breach reports from sites and third parties to establish if they meet the definition of a serious breach.
3. Reviewing serious breaches that have occurred as a result of their own quality systems, e.g. failure to follow own SOPs that impacts the safety/rights of participants or the integrity of the data.
4. Ensuring all members of the Sponsor-Investigator's central coordinating trial team know how to identify a Sponsor-level serious breach that meets the definition of a data breach in which case containment and reporting of the breach should be per MCRI's Data Breach Response Plan rather than the serious breach reporting pathway outlined in this SOP. ***Important: data breaches must be reported to databreach@mcri.edu.au within two hours of discovery.***
5. Capturing all serious breaches using a Central Non-Compliance Log [MCTC126] maintained within the Trial Master File (TMF).
6. Ongoing review (frequency tailored to the trial to reflect the complexity of the protocol and the nature of the intervention) of all non-compliance events to monitor for trends, e.g. recurrence of protocol deviations that lead to a serious breach, need for re-training.
7. Management of root cause analysis and CAPAs. Refer to MCTC061 SOP Continuous improvement: a corrective and preventive action (CAPA) plan [MCTC061].
8. Reporting to stakeholders. See Section 4.2.2 and 4.3.3 for details.
9. Management of essential documents relating to serious breaches, including justification for determining when a suspected breach does not meet the definition of a serious breach, in the TMF.
10. For international participating sites, ensure that the international Site Principal Investigator meets their requirement to submit serious breach reports to their reviewing ethics committee and/or Regulatory Authority, as per local regulatory requirements.

4. PROCEDURE

Please refer to Appendix 2: Workflow – Non-compliance reporting for an overview of the following procedure.

4.1. Definitions

Protocol Deviation

A protocol deviation is any breach, divergence, or departure from the requirements of Good Clinical Practice (GCP) or the clinical trial protocol that does not meet the definition of a serious breach (see

below). This definition may be expanded to include the following clarifying principles taken from TransCelerate: Protocol Deviation Process Guide:

- An event occurred (i.e. not theoretical).
- The event is related to the protocol or documents referenced in the protocol (e.g. laboratory manual).
- The event is independent of fault, blame or circumstance (e.g. participant refused a procedure, sample tube broke en route to the central laboratory).

Examples of protocol deviations include:

- Visit date outside the study visit window
- Missed or incomplete study procedure (e.g. lab test)
- Missed or incomplete study evaluation (e.g. assessment or examination)

Serious Breach

A serious breach is a breach of Good Clinical Practice (GCP) or the protocol that is likely to affect to a significant degree:

a) The safety or rights of a trial participant; and/or

b) The reliability and robustness of the data generated in the clinical trial.

Examples of serious breaches are included in Appendix 3.

Other terms referred to in this document are defined in Section 6 Glossary.

4.2. MCRI Sponsor-Investigator Reviewing & Reporting Procedure

4.2.1. Reviewing Suspected Serious Breach Reports

4.2.1.1 The MCRI Sponsor-Investigator (or delegate) should confirm receipt of Non-Compliance Report Forms sent from a site (i.e. site-level suspected serious breach) or reported at the Sponsor level as a result of non-compliance with the Sponsor's quality systems.

Note the Trial Coordinator should provide participating sites with a trial-specific Non-Compliance Report Form developed using MCRI template Non-Compliance Report Form [MCTC124].

4.2.1.2 The MCRI Sponsor-Investigator (or delegate) must review and assess the suspected breach within **24 hours of receipt** from the site to establish if it meets the definition of a serious breach. They must document their review using the Non-Compliance Review Form [MCTC125].

Note the trial-specific Non-Compliance Report Form should be developed using the MCRI template Non-Compliance Review Form [MCTC125].

4.2.1.3 The Trial Coordinator must provide a copy of the Non-Compliance Review Form completed by the MCRI Sponsor-Investigator to the site **within 24 hours** of the review being undertaken so the site can acknowledge the outcome of the review.

4.2.1.4 Once the site has returned the Non-Compliance Review Form with the Participating Site Acknowledgement section completed, the Trial Coordinator must file the completed form in the Site Information File (SIF).

4.2.2. Reporting Confirmed Serious Breaches (sponsor-level and site-level)

4.2.2.1 The MCRI Sponsor-Investigator (or delegate) must complete and submit a Serious Breach Report form to the reviewing HREC within 7 calendar days of confirmation in accordance with the requirements of the reviewing HREC. In the state of Victoria, serious breach report forms are completed and submitted within Ethical Review Manager (ERM). The Serious Breach Report is available through the HREA parent form.

4.2.2.2 If the serious breach occurred at either the Sponsor-level or a Melbourne Children's site (RCH or MCRI), a copy of the Serious Breach Report form must also be submitted to the MCRI Sponsorship Committee within 7 calendar days of confirmation by email to mctc@mcri.edu.au.

4.2.2.3 If the serious breach occurred at a site, the MCRI Sponsor-Investigator (or delegate) must notify the Site PI where the breach occurred **within 7 calendar days** of confirming the serious breach. This includes providing the site with a copy of the Serious Breach Report.

4.2.2.4 For trials involving an investigational medicinal product (IMP), the MCRI Sponsor-Investigator (or delegate) must notify the TGA (and/or other global Regulatory Bodies, as required) and the reviewing HREC if the serious breach leads to closure of a site. Note for trials conducted in Australia – relevant only if conducted under the TGA's Clinical Trial Notification (CTN) or Clinical Trial Approval (CTA) scheme.

How to notify the TGA: Notify the Pharmacovigilance and Special Access Branch via email to clinical.trials@health.gov.au without undue delay and no later than 15 calendar days of the Sponsor-Investigator/CPI becoming aware of the issue or temporary halt or early termination.

How to contact the reviewing HREC: In the state of Victoria, Site Closure Reports are completed and submitted within ERM. The Site Closure Report is available through the HREA parent form. The MCRI Sponsor-Investigator (or delegate) must notify the TGA or the Marketing Authorisation Holder/manufacturer (who would report to the TGA) of any serious breach that involves a defective product that may have wider implications for the supply chain of that marketed product.

4.2.2.5 If a serious breach has occurred at Site level, the MCRI Sponsor-Investigator may work with the Site PI/delegate to implement/approve any corrective and preventive actions (CAPA) required at the site. Refer to MCTC061 SOP Continuous improvement: a corrective and preventive action (CAPA) plan for further instructions on how to implement a CAPA plan.

4.2.2.6 If a serious breach has occurred at Sponsor-level, the reviewing HREC, and/or MCRI Sponsorship Committee, may request to review the CAPA to assess if the actions are appropriate and adequately address the issue.

4.2.3. Reviewing and reporting suspected breaches reported by third party

The MCRI Sponsor-Investigator (or delegate) may receive a third-party report of a suspected breach from the reviewing HREC. This may occur when a third party, (e.g. a participating site) submits a suspected serious breach directly to the reviewing HREC. In this circumstance, the MCRI Sponsor-Investigator (or delegate):

4.2.3.1 Should follow the steps outlined in 4.2.1.

4.2.3.2 If a serious breach is confirmed, the MCRI Sponsor-Investigator (or delegate) must follow the steps outlined in 4.2.2.

4.2.3.3 If a serious breach is not confirmed, the MCRI Sponsor-Investigator (or delegate) must notify the reviewing HREC by letter or email, including a justification for this decision, **within 7 calendar days** of making their decision.

4.2.4. Recording serious breaches in the Trial Master File

4.2.4.1 The MCRI Sponsor-Investigator (or delegate) must capture all serious breaches on a Central Non-Compliance Log [MCTC126] maintained within the Trial Master File (TMF).

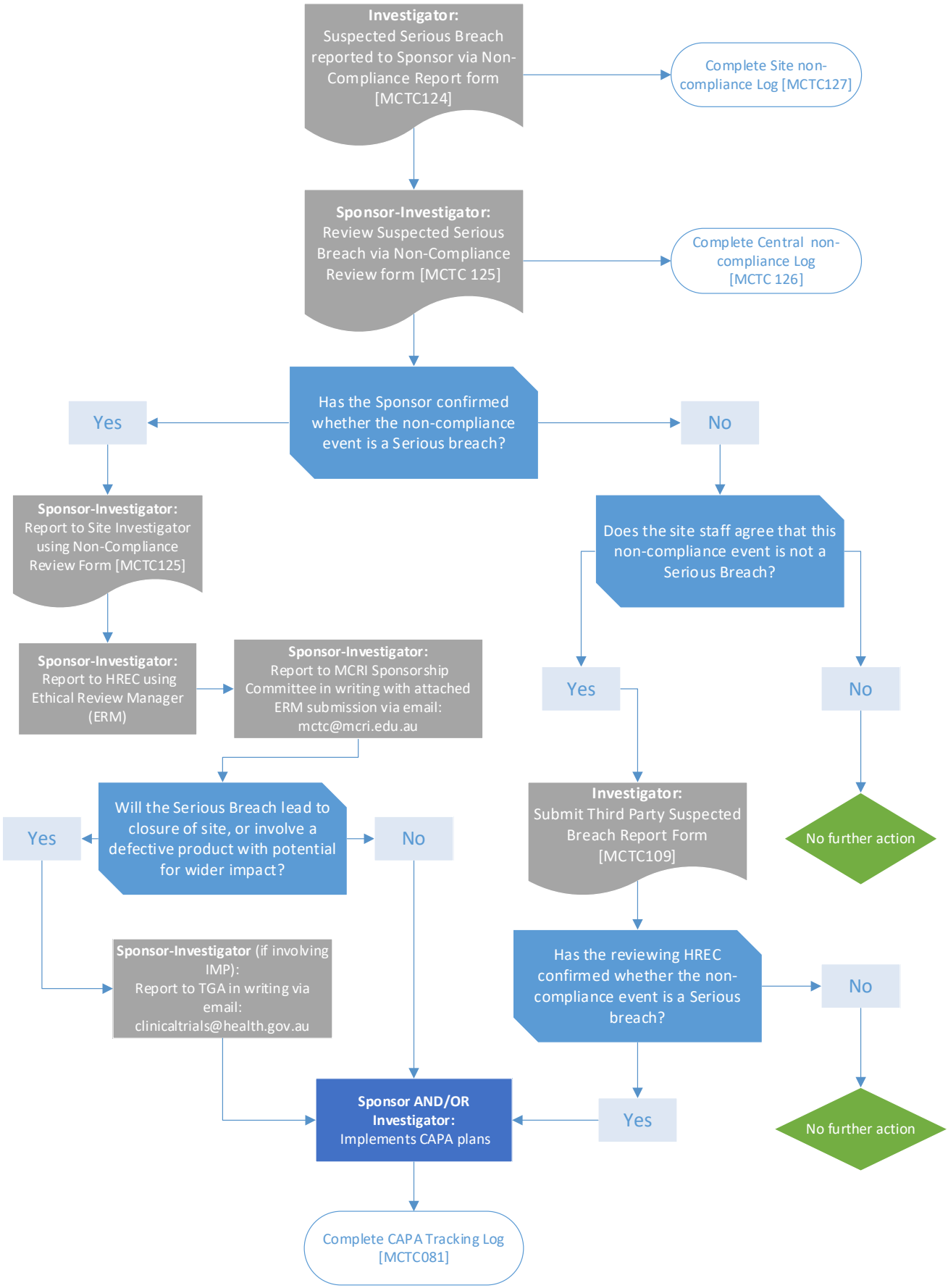
4.2.4.2 The MCRI Sponsor-Investigator (or delegate) must retain all correspondence regarding the receipt, review, reporting and recording of serious breaches and CAPAs within the TMF.

5. APPENDICES

Appendix 1: Summary of Serious and Suspected Serious Breach Reporting Requirements

Reporting Party	Report Required & Timeline	Supporting Information Required
Sponsor or delegate	**Serious breaches** should be notified to the HREC within **7 calendar days** of the sponsor confirming that a serious breach has occurred	Complete and submit a Serious Breach Form via ERM; include: 1. Details of the serious breach 2. Impact of the serious breach on any of: - Participant safety - Participant rights - Reliability and robustness of data 3. Details of any action taken to date: - Investigations being conducted - Outcome of investigations - How the serious breach will be reported in publications - CAPA plan to be developed and implemented
Sponsor or delegate	Notify the reviewing HREC and TGA (if applicable) if a serious breach leads to the closure of a site.	Complete and submit a Site Closure Report via ERM and include: 1. Reason for closure of site 2. Ongoing plan for site participants 3. Implications for other sites, if any
Site Principal Investigator	**Serious breaches** should be notified to **the Sponsor** within **72 hours** of becoming aware of the suspected breach	Complete a Non-Compliance Report Form [MCTC124] and email direct to the Sponsor. Include the following information in the form: 1. Deviation category 2. Description of the suspected serious breach 3. CAPA plans both taken and planned
Third Party	The PI/institution may report a serious breach directly to the reviewing HREC within 48 hours of receiving the response from the Sponsor if: • the sponsor disagrees with their assessment and is unwilling to contact the HREC • They are aware the Sponsor may have committed a serious breach	Complete a Third Party Suspected Breach Report Form [MCTC109] and email direct to the reviewing HREC. Include the following information in the form: 1. Details of the suspected serious breach 2. Impact of the serious breach on any of: - Participant safety - Participant rights - Reliability and robustness of data 3. Explanation of where, how, and when the suspected breach was identified

Appendix 2: Workflow - Non-compliance Reporting



Appendix 3: Examples of Serious Breaches

Adapted from The University of Manchester "Reporting a Serious Breach SOP – Version 5.0; dated: March 2018.

Notified By	Breach Type *(Site-Level /Sponsor-Level)*	Breach Description	Is the Breach considered a Serious Breach?
Sponsor	Site-Level	Dosing error. Ethics Committee & RGO informed. Participant/s withdrawn. The sponsor stated that there were no serious consequences to participants or data.	No. As no significant impact on the integrity of trial participants or on scientific validity of the trial.
Sponsor	Site-Level	Participant Information Sheet and Informed Consent updated. At one trial site this was not relayed to the participants until approximately 2-3 months after approval. More information on the potential consequences of the delay should have been provided.	Possibly not. If this was not a systematic or persistent problem and if no harm to trial participants resulted from the delay. Yes, if there was a significant impact on the integrity of trial participants (e.g., there was key safety information not relayed to participants in a timely manner etc).
Sponsor	Site-Level	Visit date deviation. *Note: A common deviation in clinical trials.*	No. A minor protocol deviation, which does not meet the criteria for notification.
Site Investigator	Site-Level	Investigator failed to report a single SAE as defined in the protocol (re-training provided).	No, if it did not result in this or other trial participants being put at risk, and if it was not a systematic or persistent problem. In some circumstances, failure to report a SUSAR could have a significant impact on trial participants. Sufficient information and context should be provided for the impact to be assessed adequately.
Identified during inspection	Site-Level	Investigator site failed to reduce or stop trial medication, in response to certain laboratory parameters, as required by the protocol. This occurred with several participants over a one-year period, despite identification by the monitor of the first two occasions. Participants were put at increased risk of thrombosis.	Yes, there was potential for significant impact on the safety or rights of trial participants.
Sponsor	Site-Level	Investigational Medicinal Product (IMP) temperature excursions reported	No, if the excursions had been managed appropriately (i.e., IMP moved to alternative location/quarantined as necessary and it was identified by qualified personnel that there was no impact on stability

Notified By	Breach Type *(Site-Level /Sponsor-Level)*	Breach Description	Is the Breach considered a Serious Breach?
			of the product and therefore no impact on participant safety/data integrity). Yes, if this went unmanaged and participants were dosed with IMP found to have become unstable and this resulted in harm or potential harm to participants.
Sponsor	Site-Level	On two separate occasions Sponsor identified issues with the same organisation. First with consenting issues and the second with potential fraud in recruitment and consenting. However, there was not unequivocal evidence of fraud at the time of reporting. One of the studies involved children.	Yes, this subsequently led to enforcement action against the organisation in question.
Sponsor-Investigator	Sponsor-Level	A cohort had invalid blood samples as they were processed by the trial's central lab incorrectly. As a result, one of the secondary endpoints could not be met. Therefore, a substantial amendment was required to recruit more participants to meet the endpoint. Participants were dosed unnecessarily as a result of this error.	Yes
Sponsor	Site-Level	A pharmacy dispensing error resulted in a non-serious adverse event. The incident was investigated and the notification from the Sponsor confirmed that training had occurred, and more robust procedures were being implemented by the site.	No, information provided by the Sponsor identified this as a single episode and the Sponsor supplied detailed CAPA plan Yes, if it was persistent and systematic, occurring after the CAPA had been put in place by the Sponsor.
Identified during inspection.	Sponsor-Level	A potential serious breach was identified, but not reported (i.e., documentation in the Sponsor's TMF identified that there may have been fraud at an investigator site, re-use of previous timepoint data in later timepoints). The Sponsor had investigated, and the issue was subsequently found to be a genuine error not fraud.	No, on this occasion. However, had this been identified as fraud impacting on the integrity of the data, then this serious breach would not have been notified within the regulatory timeframe (i.e., 7-day window).
Sponsor	Site-Level	Destruction of investigator site files early (i.e., one study had only been completed a year earlier and one study was still on-going.)	Yes

Notified By	Breach Type *(Site-Level /Sponsor-Level)*	Breach Description	Is the Breach considered a Serious Breach?
Sponsor	Site-Level	Concerns raised during monitoring visits about changes to source data for a number of participants in a trial, which subsequently made participants eligible with no explanation. An audit was carried out by the Sponsor and other changes to source data were noted without explanation, potentially impacting on data integrity. Follow-up reports sent to Competent Authority confirmed Sponsor concerns over procedures for approvals, consenting issues and data changes made to source without adequate written explanation.	Yes
Monitor	Site-Level	Participant safety compromised as, protocol not followed and, therefore, repeat ECGs were not conducted when required. Also, potential stopping criteria missed due to inadequate QC of the interim clinical summary report for dose escalation.	Yes
Sponsor	Site-Level	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.
Sponsor	Site-Level	On three occasions a site failed to see a participant within the protocol specified visit window.	No, the deviation had minimal impact on participant safety or data reliability/robustness.
Site Principal Investigator	Sponsor-Level	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

Notified By	Breach Type *(Site-Level /Sponsor-Level)*	Breach Description	Is the Breach considered a Serious Breach?
Sponsor	Sponsor-Level	Regulatory Authority (e.g. TGA) notified that a substantial amendment had been submitted regarding changes to dosing on a first in human study, as a result of an SAE after dosing the initial subject. The sponsor had temporarily halted the trial and only after further investigation had assigned the SAE as unrelated. The sponsor-investigator had not notified the Regulatory Authority of the "urgent safety measure" implemented or reported the SAE as a potential SUSAR.	Yes

6. GLOSSARY

Case Report Form (CRF)
Data collection tool used to record all of the protocol required information to be reported to the sponsor on each research/trial participant. The CRF may be paper or electronic.

Clinical Trial
The World Health Organization (WHO) definition for a clinical trial is: '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'.

Clinical Trial Approval (CTA)
Formally known as Clinical Trial Exemption (CTX), one of two schemes used by the Therapeutic Goods Administration (TGA) to authorise the supply of unapproved therapeutic goods, including medicines, medical devices, and biologicals, to participants participating in clinical trials in Australia.

The CTX scheme is appropriate for trials where the reviewing ethics committee does not have access to the appropriate scientific and technical expertise to review the trial under the CTN scheme. It is generally used for high risk or novel treatments, such as gene therapy, where there is no or limited knowledge of safety.

Clinical Trial Notification (CTN)
One of two schemes used by the Therapeutic Goods Administration (TGA) to authorise the supply of unapproved therapeutic goods, including medicines, medical devices, and biologicals, to participants participating in clinical trials in Australia.

The CTN scheme is appropriate for trials where the reviewing ethics committee has enough scientific and technical expertise to review the proposed use of the unapproved therapeutic good(s). The majority of investigator-initiated trials would be in this category.

Collaborative Research Group
An academic and/or non-commercial collaborative research group responsible for sponsoring, initiating, managing, developing, and coordinating a research study/trial.

Corrective and Preventive Action Plan
A Corrective and Preventive Action (CAPA) plan is a quality system plan and incorporates:

1. Identifying the issue, including scope and impact
2. Identifying the root cause of the issue – how/why it occurred
3. Identifying actions to prevent recurrence of the issue (corrective action) or, identify actions to prevent an issue from occurring (preventive action)
4. Documenting that the corrective actions/preventive actions were completed
5. Documenting that the corrective/preventive action has resolved the problem

Data Breach

An incident, in which information is compromised, disclosed, copied, transmitted, accessed, removed, destroyed, stolen or used by unauthorised individuals, whether accidentally or intentionally. Examples include:

- Laptops, USB, hard drive containing data being lost or stolen;
- Paper records being lost or stolen

- Data being accessed or disclosed by staff operating outside the scope of their work
- Staff mistakenly sending test results or research data to the wrong email address
- Databases containing data being 'hacked' or otherwise illegally accessed by contractor, or other individuals outside of the MCRI

Essential Documents
Documents which individually and collectively permit evaluation of the conduct of a study and the quality of the data produced. These documents serve to demonstrate the compliance of the Investigator, Sponsor and monitor with the standards of Good Clinical Practice (GCP) and with all applicable regulatory requirements. Filing essential documents at the Sponsor site and participating trial sites also assists with the successful management of the trial.

Good Clinical Practice (GCP)
A standard for the design, conduct, performance, monitoring, auditing, recording, analyses, and reporting of clinical trials that provides assurance that the data and reported results are credible and accurate, and that the rights, integrity, and confidentiality of trial participants are protected.
HREC
Human Research Ethics Committee

Investigator
A person responsible for the conduct of the clinical trial at a trial site. There are three types of Investigator roles used to describe Investigators with different levels of responsibility for the conduct of clinical trials. These are described below.

Associate Investigator
Any individual member of the clinical trial team designated and supervised by the investigator at a trial site to perform critical trial-related procedures and/or to make important trial-related decisions (e.g., associates, residents, research fellows). May also be referred to as sub-investigator.

Principal Investigator
The PI is the person responsible, individually or as a leader of the clinical trial team at a site, for the conduct of a clinical trial at that site. As such, the PI supports a culture of responsible clinical trial conduct in their health service organisation in their field of practice and, is responsible for adequately supervising his or her clinical trial team.

The PI must conduct the clinical trial in accordance with the approved clinical trial protocol and ensure adequate clinical cover is provided for the trial and ensure compliance with the trial protocol.

Sponsor-Investigator / Coordinating Principal Investigator (CPI)
In investigator-initiated and collaborative research group trials, the Principal Investigator taking overall responsibility for the study and for the coordination across all sites (if it is a multi-centre trial) is known as the Sponsor-Investigator or Coordinating Principal Investigator (CPI). In this case, the Sponsor will delegate many sponsor responsibilities to the Sponsor-Investigator/Sponsor-Investigator.

Investigator-Initiated Trials (IITs)
A clinical trial which is initiated and organised by an Investigator i.e. an individual rather than a collaborative group, company, or organisation. In these cases, the Investigator will take on the role of the trial sponsor and will then be responsible for the extensive GCP and regulatory requirements associated with both the management and conduct of the trial.

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 authorization when used or assembled (formulated or packaged) in a way different from the approved form, or when used for an unapproved indication, or when used to gain further information about an approved use.

Investigational Medical Device (IMD)
A device that is the subject of a clinical study designed to evaluate the effectiveness and/or safety of the device.

Investigator Site File (ISF)
Filing repository controlled by the site Principal Investigator. It is held at the trial site and contains all the essential documents necessary for the site trial team to conduct the trial as well as the essential documents that individually and collectively permit evaluation of the conduct of the trial at the site and the quality of the data produced.

Monitor
A person appointed by the Sponsor to undertake the role of monitoring for the trial. Monitors should be appropriately trained and should have the scientific and/or clinical knowledge needed to monitor the trial adequately.

MCRI
Murdoch Children's Research Institute

Melbourne Children's Trials Centre (MCTC)
Melbourne Children's Trials Centre (MCTC) is a collaboration between the Royal Children's Hospital, The Murdoch Children's Research Institute, The Royal Children's Hospital Foundation and The University of Melbourne.

Non-Compliance Report Form
Used by sites participating in MCRI-sponsored IITs to report non-compliance with protocol or GCP to the Sponsor-Investigator/CPI when their assessment suggests a serious breach has occurred.

Non-Compliance Review Form
Used by Sponsor-Investigator/CPI to review non-compliance report Forms submitted by participating sites. Form documents the review and assessment of whether the Sponsor-Investigator/CPI determines the non-compliance to meet the definition of a serious breach.

Participant
A participant is a person that is the subject of the research.

Pharmacovigilance
Process of ongoing monitoring of the safety profile, combined with the ongoing assessment and evaluation of the risk-benefit of medicines. The process is important to identify adverse reactions/adverse device effects and changes in the known safety profile.

Research Ethics and Governance Office (REG)
REG supports the HREC and institutional research governance processes at MCRI.

Serious Adverse event (SAE)

An adverse event is defined as **serious** if it:

- results in death
- is life-threatening
- requires hospitalisation or prolongation of existing hospitalisation
- results in persistent or significant disability or incapacity
- is a congenital anomaly or birth defect

Other important medical events will be considered an SAE when, based upon appropriate medical judgment, they may jeopardize the research participant and may require medical or surgical intervention to prevent one of the outcomes listed in the above definition. This can include diagnosis of cancer.

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

Sponsor
An individual, organisation or group taking on responsibility for securing the arrangements to initiate, manage and finance a study. For investigator-initiated trials, MCRI or RCH will act as the Sponsor but delegate many sponsor responsibilities to the Coordinating Principal Investigator. In this case the CPI has the role of both Sponsor and Investigator and hence the MCTC has adopted the term **Sponsor-Investigator** to reflect the dual role of the CPI in investigator-initiated trials.

Standard Operating Procedure (SOP)
Detailed, written instructions to achieve uniformity of the performance of a specific function.

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.

Suspected Unexpected Serious Adverse Reaction (SUSAR)
This is a serious adverse event:

- Where there is at least a reasonable possibility of a causal relationship between an intervention and an adverse event (in other words the relationship of the SAE to the trial drug/device/other intervention cannot be ruled out)
  and
- That is unexpected, meaning that the nature or severity of the reaction is not consistent with the known scientific information (e.g. Investigator's Brochure for an unapproved investigational product or product information document or similar for an approved, marketed product)

The National Health and Medical Research Council (NHMRC)

NHMRC is Australia's leading expert body for: supporting health and medical research; developing health advice for the Australian community, health professionals and governments; and providing advice on ethical behaviour in health care and in the conduct of health and medical research.

Therapeutic Good
In relation to the evaluation, assessment and monitoring done by the TGA, therapeutic goods are broadly defined as products for use in humans in connection with:

- preventing, diagnosing, curing, or alleviating a disease, ailment, defect, or injury
- influencing inhibiting or modifying a physiological process
- testing the susceptibility of persons to a disease or ailment
- influencing, controlling, or preventing conception
- testing for pregnancy

This includes things that are:

- used as an ingredient or component in the manufacture of therapeutic goods
- used to replace or modify of parts of the anatomy

Therapeutic Goods Administration (TGA)
The Therapeutic Goods Administration (TGA) is Australia's regulatory authority for therapeutic goods.

Third Party
Any entity (other than the trial Sponsor) wishing to report a suspected serious breach.

Third Party Suspected Breach Report Form
Form used by sites to directly notify the reviewing HREC of a suspected serious breach. This route is uncommon and used if the Sponsor disagrees with the site assessment that a serious breach has occurred.

Trial Master File (TMF)
Filing repository controlled by the Sponsor/Sponsor-Investigator. It is the collection of essential documents that allows the Sponsor responsibilities for the conduct of the clinical trial, the integrity of the trial data and the compliance of the trial with Good Clinical Practice (GCP) to be evaluated.

7. REFERENCES

- Department of Health and Human Services Victoria, Coordinating Office for Clinical Trial Research Information on multi-site reporting requirements for trials can be found in "Research governance and Site specific assessment – process and practice" available at http://www.health.vic.gov.au/clinicaltrials/site-specific.htm
- National Health and Medical Research Council (2018), Reporting of Serious Breaches of Good Clinical Practice (GCP) or the Protocol for Trials Involving Therapeutic Goods, available at https://www.nhmrc.gov.au/about-us/publications/safety-monitoring-and-reporting-clinical-trials-involving-therapeutic-goods
- TGA Guidance: Australian Clinical Trial Handbook: Guidance on conducting clinical trials in Australian using "unapproved" therapeutic goods, Version 2.2 October 2018, available at https://www.tga.gov.au/publication/australian-clinical-trial-handbook
- TGA Integrated Addendum to ICH E6 (R1): Guideline for Good Clinical Practice ICH E6 (2) 2016 – Annotated with TGA comments available at https://www.tga.gov.au/publication/note-guidance-good-clinical-practice
- The Royal Children's Hospital Research Ethics and Governance Office reporting guidelines for protocol deviations and serious breaches available at https://www.rch.org.au/ethics/existing-applications/deviations/
- TransCelerate: Protocol Deviation Process Guide

8. ASSOCIATED DOCUMENTS

- MCTC061 SOP Continuous improvement: a corrective and preventive action (CAPA) plan
- MCTC080 CAPA template
- MCTC081 Site CAPA Tracking Log
- MCTC109 Third Party Suspected Breach Report Form
- MCTC112 MCRI/RCH Site Principal Investigator Management of Non-Compliance: Protocol Deviations and Serious Breaches
- MCTC124 Non-Compliance Report Form
- MCTC125 Non-Compliance Review Form
- MCTC126 Central Non-Compliance Log
- MCTC127 Site Non-Compliance Log

DOCUMENT END