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

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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]

This SOP describes the procedures for MCRI/RCH Site Principal Investigators (PIs) to report protocol deviations and serious breaches to the Sponsor and the RCH Research Governance Office. **Note the Sponsor may be MCRI or an external Sponsor**.

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) 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 all staff involved in conducting trials at MCRI at the Site level: Site PI, Associate/Sub-Investigator(s), research coordinator and other staff involved in research duties. The Site PI is directly responsible for implementing the procedures set out in this SOP within their study team.

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 Sponsor-Investigator Management of Non-Compliance: Protocol Deviations and Serious Breaches [MCTC123].

MCRI Site PI responsibilities include:

1. Ensuring all members of the MCRI/RCH trial team know how to identify a serious breach and escalate them to both the Sponsor for assessment and the RCH Research Ethics & Governance Office.
2. Ensuring all members of the MCRI/RCH trial team know how to identify a local 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.***
2. Capturing all deviations of the protocol (and associated procedures) and GCP that are linked to a participant within the CRF and on a Site Non-Compliance Log. See Section 4.2.1 for details.
3. Identifying when a deviation potentially meets the definition of a serious breach. At this stage in the assessment, a potential serious breach is termed a 'suspected breach'.
4. Reporting serious breaches to stakeholders. See Section 4.2.2 for details.
5. Working with the RCH Research Ethics & Governance Office and Sponsor/Sponsor-Investigator to develop and implement CAPA plan. Considering whether the issue could also impact other participants or clinical trials.
6. Managing essential documents relating to deviations and serious breaches in the Investigator Site File (ISF).

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/RCH Site PI Reporting Procedure

4.2.1. Recording Protocol Deviations

Once identified, the MCRI/RCH Site PI/delegate must record the deviation on both the Site Non-compliance Log and if the deviation relates to a trial participant, in the CRF. This log may be viewed by Monitors and regulatory Inspectors on behalf of the Sponsor and applicable regulatory authority, respectively. Usually, the Sponsor will provide the Non-Compliance Log. For MCRI-sponsored trials, use the trial-specific Site Non-Compliance Log developed using Site Non-Compliance Log [MCTC127].

4.2.2. Recording and Reporting Suspected Serious Breaches to the Sponsor and RCH Research Ethics & Governance Office

4.2.2.1 If the MCRI/RCH Site PI (or delegate) suspects that a protocol deviation may be a serious breach, they must complete the Sponsor's Non-Compliance Report Form.

For MCRI-sponsored trials, use the trial-specific Non-Compliance Report Form developed using template Non-Compliance Report Form [MCTC124].

4.2.2.2 On the Non-Compliance Report Form, the PI/delegate must provide a full description of the suspected serious breach and describe action(s) taken to both correct and prevent recurrence of the serious breach in the future.

4.2.2.3 The completed Non-Compliance Report Form must be emailed to the Sponsor/delegate **within 72 hours** of site staff becoming aware of the event.

4.2.2.4 The site must file the completed Non-Compliance Report Form in the ISF.

4.2.2.5 If the Sponsor confirms a serious breach has occurred, the MCRI/RCH Site PI/delegate must:

- Complete the PI acknowledgement section of the trial-specific Non-Compliance Review Form that has been completed and provided by the Sponsor, return a copy to the RCH/MCRI Trial Coordinator within **24-48 hours of receipt** and file a copy in the ISF.
- Forward a copy of the Serious Breach Report (provided by the Sponsor to RCH Research Ethics & Governance Office, **within 72 hours** of **being notified** using the appropriate pathway as per below:

  For MCRI/RCH site PIs of studies that have received ethics approval elsewhere (not RCH HREC): Use the Site Notification Form in ERM to submit a copy of the Serious Breach Report to the RCH Research Ethics & Governance Office as per Site Specific Authorisation conditions. Note in this circumstance, the Site PI should share the outcome of the external HREC review with the RCH Research Ethics & Governance Office.

  For MCRI/RCH site PIs where the study has been ethically approved by RCH HREC and the site PI is also acting as the Sponsor-Investigator, refer to SOP MCTC123 for how to report serious breaches to the RCH HREC.

4.2.2.6 The Site PI should work with the Sponsor, as appropriate, or RCH Research Ethics & Governance Office (if applicable) to implement any new CAPA plans that may be required at site level, taking into consideration any CAPA plans already implemented at site. Refer to SOP Continuous improvement: a corrective and preventive action (CAPA) plan [MCTC061] for the process and also Section 4.2.2.7.

4.2.2.7 In addition to the brief summary of the CAPA plan outlined in the Non-Compliance Report Form, the PI/delegate should document the CAPA plan using the MCRI CAPA plan template [MCTC080] with the exception of externally sponsored trials where the external Sponsor may require the MCRI/RCH site to use their template.

4.2.2.8 Evidence of RCH Research Ethics & Governance Office, or equivalent for International participating sites, Ethics Committee and/or Regulatory Authority acknowledgement for International participating sites (if applicable) and/or Sponsor's review and approval of the CAPA plans must be filed in the ISF.

4.2.2.9 All site CAPAs should be recorded on the site CAPA Tracking Log [MCTC081].

4.2.2.10 All correspondence associated with managing serious breaches, including CAPAs, must be retained within the ISF.

4.2.3. Recording and Reporting Suspected Serious Breaches Direct to the HREC

The MCRI/RCH Site PI should follow the steps outlined in Sections 4.2.3.1 to 4.2.3.4 if the Sponsor disagrees with the MCRI/RCH Site PI's assessment that a serious breach has occurred after following the steps outlined in Sections 4.2.2.1 to 4.2.2.4, and the Site PI's opinion has not changed.

4.2.3.1 Report the suspected breach directly to the reviewing HREC using the Third Party Suspected Breach Report Form [MCTC109] **within 48 hours** of receiving the response from the Sponsor, in accordance with the requirements of the reviewing HREC.

4.2.3.2 Email a copy of the Suspected Serious Breach Report Form (Third Party) to the RCH Research Ethics & Governance Office, **within 72 hours** of receiving the response from the Sponsor.

4.2.3.3 Follow the instructions of the reviewing HREC or the Sponsor, as appropriate, or RCH Research Ethics & Governance Office (if applicable) to implement any CAPA plan that may be required at site level, taking into consideration any CAPA plan already implemented at site. See Section 4.2.2.6 and 4.2.2.7

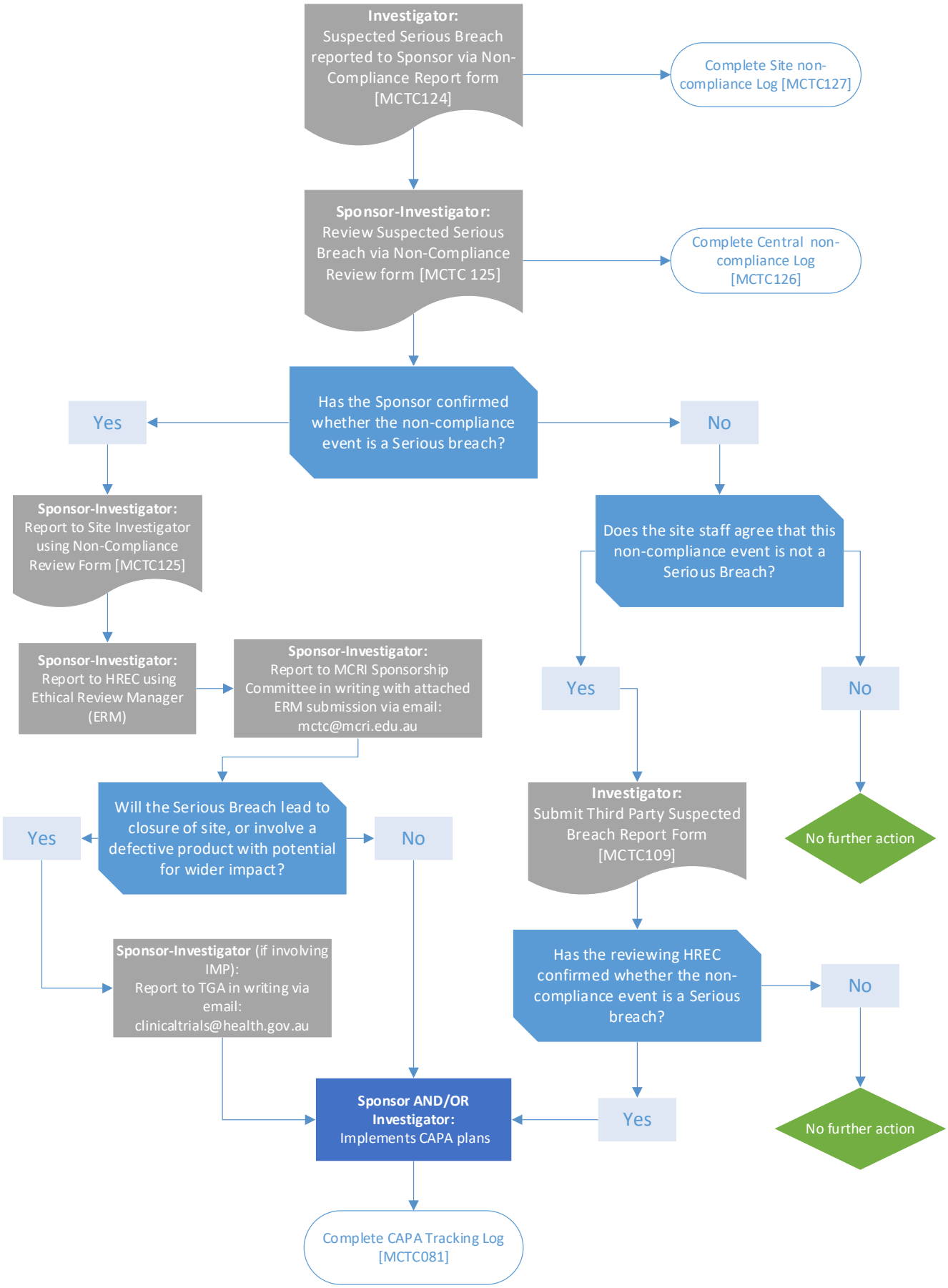
4.2.3.4 In addition to the brief summary of the CAPA plan outlined in the Non-Compliance Report Form, the PI/delegate should document the CAPA plan using the MCRI CAPA plan template [MCTC080] with the exception of externally sponsored trials where the external Sponsor may require the MCRI/RCH site to use their template.

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

Notified By	Breach Type *(Site-Level /Sponsor-Level)*	Breach Description	Is the Breach considered a Serious Breach?
			location/quarantined as necessary and it was identified by qualified personnel that there was no impact on stability 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).

Notified By	Breach Type *(Site-Level /Sponsor-Level)*	Breach Description	Is the Breach considered a Serious Breach?
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
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. The deviations were a consequence of unnecessarily narrow inclusion criteria, which was rectified through a protocol amendment.
Sponsor	Site-Level	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.
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
- MCTC123 MCRI Sponsor-Investigator Management of Non-Compliance: Protocol Deviations and Serious Breaches
- MCTC124 Non-Compliance Report Form
- MCTC127 Site Non-Compliance Log

DOCUMENT END