Procedure

Safety Reporting for Clinical Trials

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Risk Rating	High		
Primary Document	Safety Reporting for Clinical Trials		
Approval Authority	Executive Director Clinical Services	**Approval date**	14/10/2024
Author/Custodian	Human Research Ethics / Research Governance	**Effective date**	17/10/2024
Applicable to	All CHQ Staff involved with research	**Review date**	14/10/2027

HUMAN RIGHTS

This governance document has been human rights compatibility assessed. No limitations were identified indicating reasonable confidence that, when adhered to, there are no implications arising under the *Human Rights Act 2019.*

PURPOSE

Safety Reporting for clinical trials must follow the 2018 NHMRC Guidance: Safety Monitoring and Reporting in Clinical Trials Involving Therapeutic Goods[1] and the Reporting of Serious Breaches of Good Clinical Practice (GCP) or the Protocol for Trials Involving Therapeutic Goods[2]. All Safety Reporting must be submitted via the Ethics Review Manager (ERM) web portal [ethicalreviewmanager.com] for researchers, by creating a sub-form under the relevant project and application form.

SCOPE

This guideline applies to all staff who are involved with research approved by CHQ Human Research Ethics Committee (HREC) and CHQ Research Governance (RGO).

PROCEDURE

Type of Report	Reporting Requirement		
	Report to CHQ HREC **When CHQ is the reviewing HREC**	**Report to RGO*** **When CHQ is the accepting site (RGO only)**	**Sponsor** **When CHQ is the Sponsor** **Report to RGO**
Urgent Safety Measures (USMs)	72 hours of becoming aware of the event.	72 hours of becoming aware of the event.	24 hours of becoming aware of the event.
Significant Safety Issues (SSIs)	15 calendar days of the sponsor instigating or being made aware of the issue.	SSI resulting in temporary halt, amendment or early termination of a trial within 72 hours of becoming aware of the event.	72 hours of becoming aware of the event.
Suspected Unexpected Serious Adverse Reactions (SUSARs) or Unanticipated Serious Adverse Device Effects (USADEs)	Not required. Ensure event is reported to sponsor and DSMB. Include in annual safety report.	72 hours of becoming aware of the event, or change in status from SAE (Serious Adverse Event) to SUSAR. From the local site.	72 hours of becoming aware of the event, or change in status from SAE (Serious Adverse Event) to SUSAR.
Serious Adverse Event (SAE) **Excluded events identified in the protocol as not requiring immediate reporting**	Not required. Ensure event is reported to sponsor and DSMB. Include in annual safety report.	Not required unless the event is directly connected to the study treatment.	24 hours of becoming aware of the event.
Please submit to both CHQ HREC and RGO - All safety reports for participants where it is thought the event is directly connected to the study treatment. This does not include expected events as per the Protocol/Information Sheet.			
Protocol deviations/violations	If thought to impact the safety of the participant or study	If thought to impact the safety of the participant or study	If thought to impact the safety of the participant or study
Annual Safety Reporting	Annually	Annually	Annually
Investigator Brochure amendment	As changes are made	Not required	As changes are made, notify HREC approval
Data Safety Monitoring Board (DSMB) reports	As available	As available	As available

* Ensure report to lead HREC

For submission to the CHQ Research Governance Office via ERM portal [ethicalreviewmanager.com] AND send an email to the RGO [cqh_rgo@health.qld.gov.au] with the subject line **'Safety Report'** and attach the completed report

Refer to Appendix 1 & 2 for reference documents for report safety and corrective action.

THERAPEUTIC GOODS ADMINISTRATION (TGA) AND OTHER REGULATORY REPORTING FOR CHQ SPONSORED CLINICAL TRIALS

The Principal Investigator is delegated the responsibility to report to the TGA or any other regulatory authority. The principal investigator or delegate must notify the CHQ RGO as sponsor of any reporting that has taken place. Therapeutic Goods Administration (TGA) | Australian Government Department of Health

Note:

For safety reporting definitions please reference NHMRC Safety monitoring and reporting in clinical trials involving therapeutic goods[1] (page4, PART 1, A). For further questions please contact CHQ RGO [chq_rgo@health.qld.gov.au]

CLINICAL INCIDENT MANAGEMENT

Any staff member who identifies that a clinical incident has occurred has a duty to act. A clinical incident is a healthcare event or circumstance which could have resulted or did result in unintended harm to the patient/ participant. Staff should consider if the safety event being report to HREC/RGO requires reporting in the incident management system. Incident reporting is available on QHEPS. Please refer to the CHQ Clinical Incident Management[3] policy for further instructions.

SUPPORTING DOCUMENTS

Standards:

- 2018 NHMRC Guidance: Safety Monitoring and Reporting in Clinical Trials Involving Therapeutic Goods[1]
- Reporting of Serious Breaches of Good Clinical Practice (GCP) or the Protocol for Trials Involving Therapeutic Goods[2]
- 2023 Children's Health Queensland Clinical Incident Management

CONSULTATION

Key stakeholders who reviewed this version:

• Director of Research • Chair, CHQ HREC • Co-ordinator, CHQ HREC • Senior Manager research Services and Partnerships	• Research Governance Office • Research Compliance and Monitoring Office • Program Manager Advanced Therapies

DEFINITIONS

Term	Definition
Adverse Event (AE)	Any untoward medical occurrence in a patient or clinical trial participant administered a medicinal product and that does not necessarily have a causal relationship with this treatment.[1]
Data Safety Monitoring Board (DSMB	An independent and multidisciplinary group established by the trial sponsor to review, at intervals, accumulating trial data, in order to monitor the progress of a trial and to make recommendations on whether to continue, modify or stop the trial for safety or ethical reasons[4]
Investigator's Brochure (IB)	The document containing a summary of the clinical and non-clinical data relating to an investigational medicinal product that are relevant to the study of the product in humans[1]
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.[4]
Serious Adverse Event (SAE)	Any adverse event/adverse reaction that results in death, is life-threatening, requires hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, or is a congenital anomaly or birth defect.[1]
Significant Safety Issue (SSI)	A safety issue that could adversely affect the safety of participants or materially impact on the continued ethical acceptability or conduct of the trial.[1]
Sponsor	An individual, organisation or group taking on responsibility for securing the arrangements to initiate, manage and finance a study.[4]
Suspected Unexpected Serious Adverse Reaction (SUSAR)	An adverse reaction that is both serious and unexpected.[1]
Unanticipated Serious Adverse Device Effect (USADE)	Serious adverse device effect which by its nature, incidence, severity or outcome has not been identified in the current version of the risk analysis report Note: Anticipated serious adverse device effect (ASADE) is an effect which by its nature, incidence, severity or outcome has been identified in the risk analysis report.[1]
Urgent Safety Measure (USM)	A measure required to be taken in order to eliminate an immediate hazard to a participant's health or safety. Note: This type of significant safety issue can be instigated by either the investigator or sponsor and can be implemented before seeking approval from HRECs or institutions.

REFERENCES

No.	Reference
1	National Health and Medical Research Council (2018). Guidance: Safety monitoring and reporting in clinical trials involving therapeutic goods. Canberra: National Health and Medical Research Council.
2	National Health and Medical Research Council (2018). Reporting of Serious Breaches of Good Clinical Practice (GCP) or the Protocol for Trials Involving Therapeutic Goods. Canberra: National Health and Medical Research Council.
3	Children's Health Queensland (2023). Clinical Incident Management. Retrieved from: CHQ-PROC-00200 Clinical Incident Management (health.qld.gov.au)
4	Data Safety Monitoring Boards (DSMBs) (nhmrc.gov.au)

ASSURANCE STRATEGY

Strategy	Safety Event Board Reporting undertaken quarterly.

Audit/review tools	Audit/review tools frequency	Key performance indicator
ERM Reporting	Upon receipt	N/A
REDCap database	Upon receipt	Quarterly reporting

PROCEDURE REVISION AND APPROVAL HISTORY

Version No.	Modified by	Amendments authorised by	Approved by	Comments
1.0	HREC Coordinator	Business Manager Research	17/08/2021	
2.0 10/10/2024	Research and Clinical Trials Monitoring and Compliance Officer	Director Research	Executive Director Clinical Services	Unscheduled review and transition to new template

Key words	safety reporting, NHMRC, CHQ HREC, clinical trials, 90024
Accreditation references	The National Clinical Trials Governance Framework: • Standard 1

Queensland Government

Children's Health Queensland

Appendix 1 Report of adverse / safety event

Protocol no.	insert number
ERM Project Number:	insert number
Protocol title:	insert title of project
Sponsor:	insert name

Patient (Initials or Record No. only)	if appliciable

Report	Initial ☐ Follow up ☐

Date of adverse / safety event	dd / mm / yyyy
Date team became aware of event	dd / mm / yyyy

Description of adverse / safety event
insert details

ADVERSE EVENTS			
AE Term Please use Common Terminology Criteria for Adverse Events (CTCAE) (cancer.gov)			
AE Grade Please use Common Terminology Criteria for Adverse Events (CTCAE) (cancer.gov)			
AE Relationship to Study Intervention (Refer to below table)	☐ Definite ☐ Probable ☐ Possible ☐ Unlikely ☐ Not Related ☐ Unknown	**Is this a Serious AE?**	☐ Resulting in Death ☐ Is Life-threatening ☐ Required hospitalisation or prolongation of hospitalisation. ☐ Resulting in persistent or significant disability or incapacity ☐ Consists of a congenital abnormality or birth defect

Outcome:

Investigator's summary and comments	**Yes**	**No**

Has the study sponsor been notified?	☐	☐
Has the safety event been entered into RISKMan? If no, why not?	☐	☐
In the light of the event, is a change required to the Participant Information Sheet and / or other research documentation?	☐	☐
If yes, will already enrolled patients be re-consented? If no, why not?	☐	☐
Investigator comments[1]:		

References: National Statement on Ethical Conduct in Human Research (2023), Australian Code for the Responsible Conduct of Research (2018)

Note: If any changes to the study are required these must be submitted to the HREC and RGO for approval.

Name of Principal Investigator:	
Signature of Principal Investigator:	
Date signed:	/ /

Relationship of Adverse Events to Intervention

Relationship	Description
Definite	A reaction that follows a reasonable temporal sequence from intervention administration that follows a known or expected response pattern to the intervention and that is confirmed by improvement on stopping or reducing the intervention or reappearance of the reaction on repeated exposure.
Probable	A reaction that follows a reasonable temporal sequence from intervention that follows a known or expected response pattern to the suspected intervention that is confirmed by stopping or reducing the dosage of the intervention and that could not be reasonably explained by the known characteristics of the subject's clinical state.
Possible	A reaction that follows a reasonable temporal sequence from administration of the intervention that follows a known or expected response pattern to the suspected intervention but that could readily be produced by a number of other factors.
Unlikely	An event that does not follow a reasonable temporal sequence from intervention that does not follow a known or suspected response pattern to the intervention and that could reasonably be explained by known characteristics of the subject's clinical state.
Not Related	Any event that does not meet the above criteria.

[1] The Human Research Ethics Committee requires the Principal Investigator's comments on (a) whether the event was caused by the study drug-intervention, and (b) whether in the light of the event, changes need to be made to the already approved Patient Information and Consent Form and/or other study documentation.

Appendix 2 Corrective and Preventive Action Plan (CAPA) Template

Research teams must identify, evaluate, and respond to deviations and unexpected events to protect the rights, safety, and welfare of participants and others and the integrity of the research data.

Conducting a Root Cause Analysis

It is important to identify the cause or source of a deviation or problem to prevent a recurrence. There may be multiple reasons or causes that contribute to a problem. Conversely, there may be multiple methods to resolve each cause. The root cause is the initiating, most basic cause of a problem that may or may not lead to a chain of causes or other problems. Eliminating the root cause should prevent a recurrence.

A root cause analysis (RCA) is the process of identifying and documenting the root cause and the downstream. An RCA should focus on identifying underlying problems that contribute to error rather than focusing on mistakes made by individuals.

Steps:

1. Identify the problem	2. Interview those impacted by the problem	3. Interview those people responsible for the problem, if applicable

Questions to identify root causes:

1. What happened? What is the problem?
2. Why and how did the problem occur? What were the steps?
3. Who was affected by the problem? Was it one subject or all subjects in the study?
4. What is the magnitude of the problem? Is it in one study, or does the problem exist in all studies under this PI or in this clinical/research department?
5. Keep asking "why" and "how" until you reach the root cause.

Once you have identified the root cause, your next step is to develop a corrective and preventive action plan to eliminate the root cause.

Prepare the CAPA Plan

Corrective actions are those taken to resolve a problem, and preventive actions are those actions that keep the problem from recurring.

Corrective Actions

Consider additional reporting to the sponsor and HREC/RGO include the CAPA plan in the report.
Consider clinical reporting in RISKMan.

Preventive Actions

Preventive actions are necessary to ensure that the problem does not reoccur. An example, create and document a process or standard operating procedure (SOP). Then, train on the process, implement the process, evaluate the process, and amend the process as necessary. Consider whether you need to revise the protocol or informed consent forms as a part of your plan.

Document the CAPA Plan

CAPA plans must be thorough and well documented. In your plan, include information that is:

- Specific: Identify the actions you or others will take to address the root cause, the individual (role) responsible for taking the actions, and where you will document the actions.
- Timely: Include the date(s) when you or others will complete the actions.
- Measurable: Include a process of assessing the action plan effectiveness and a process by which the plan will be amended if it is ineffective.

A thorough CAPA plan must also include the following elements:

1. Action type (corrective or preventive)	2. Action description	3. Responsible person
4. Due date	5. Plan for effectiveness check	6. Effectiveness check outcomes

You must create and maintain documentation that demonstrates that you implemented the CAPA plan.

Corrective and Preventive Action Plan

Remove green text after completion of plan.

Date:	*Date that the CAPA is written*
Author (Person responsible for overall CAPA):	*Name, Title, the site/institutional affiliation of the person authoring the CAPA*
Protocol Title / Research Study:	
HREC Number:	
Issue / Deficiency Identified:	*Brief description or outline of the topic/process/problem being documented.*
Root Cause:	*The reason(s) that the issue arose. To investigate the root cause consider using available tools such as* *5 Whys* *Fishbone Diagram* *Failure Mode and Effects Analysis* *Fault Tree Analysis*
Corrective Action Plan:	*Description of the correction action(s) taken or planned by the site. If the site was instructed to perform these corrective actions (i.e. by the sponsor or monitor), indicate by whom and as of what date. If status of reports, records or data will remain incomplete or unavailable, make a statement regarding your failed attempts or describe when/how the records will be retrieved or completed.*
Implementation:	*Description of the procedures used to document resolution of the problem, the persons who are responsible for the procedures, etc.*
Effective Date of Resolution:	*Effective date for corrective action*
Preventive Action:	*Description of the preventive actions taken or planned by the site. If the site was instructed to perform these preventive actions, indicate by whom and as of what date. Preventive actions are taken to eliminate the root-cause of a potential problem, including the detection/identification of problems*
Evaluation/Follow up:	*Any plan/procedure to evaluate the implementation and completion, persons who are responsible for the evaluations, timeframe for the evaluation, etc.*

Comments:

Principal Investigator Signature: _____ Date: _____

Principal Investigator Printed Name: _____