TITLE	Safety Monitoring and Reporting in Research Policy
SETTING	All Cabrini staff, Visiting Medical Officers (VMO's) and external collaborators engaged in research activity at Cabrini

Contents

PURPOSE

To outline the procedures for the reporting and management of safety events in research at Cabrini, relating to clinical trials and other interventional studies.

DEFINITIONS

For clinical trials: As defined in the NHMRC guidance: Safety monitoring and reporting in clinical trials involving therapeutic goods (2016)

Investigational Medicinal Products (IMP) and Investigational Medical Devices (IMD)	
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. *An SSI usually requires an action, such as the reporting of an urgent safety measure, an amendment, a temporary halt or an early termination of a trial.*
Urgent Safety Measure	A measure required to be taken in order to eliminate an immediate hazard to a participant's health or safety.
Investigational Medicinal Products (IMP)	
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 authorisation when used or assembled (formulated or packaged) in a way different from the approved form, or when used for an unapproved indication, a new patient group or when used to gain further information about an approved use.
Serious Adverse Event (SAE)/Serious Adverse Reaction (SAR)	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.
Suspected Unexpected Serious Adverse Reaction (SUSAR)	An adverse reaction that is both serious and unexpected.
Adverse Events of Special Interest (AESI)	Adverse events of special interest (AESI) are events which are of scientific and medical concern specific to the sponsor's product or program, for which ongoing monitoring and rapid communication by the investigator to the sponsor may be appropriate. Such events may require further investigation to characterize and understand them**.** AESI's will be defined by the sponsor in the protocol as well as in the Participant Information Consent Form (PICF).
Investigational Medical Devices (IMD)	
Investigational Medical Device (IMD)	Medical device being assessed for safety or performance in a clinical investigation
Serious Adverse Device Effect (SADE)	An adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event.
Serious Adverse Event (SAE)	An adverse event that: a. led to death b. led to serious deterioration in the health of the participant, that either resulted in: • a life-threatening illness or injury, or • a permanent impairment of a body structure or a body function, or • in-patient or prolonged hospitalisation, or

	• medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure of a body function c. led to fetal distress, fetal death or a congenital abnormality or birth defect.
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

ROLES AND RESPONSIBILITIES

The Sponsor (commercial and investigator initiated) or their delegate

- Is responsible for the ongoing safety evaluation of the investigational product.
- Is responsible for generating safety communications.
- Should evaluate all safety information that is reported by investigators as well as safety information from other sources.
- Should determine the most appropriate arrangements for ongoing monitoring and document these for Cabrini Research Governance Office (CRGO) approval.
- Should ensure all monitors comply with Cabrini's vaccination and mask requirements.
- Should ensure the protocol clearly outlines assessment and management of risk, and safety reporting parameters and responsibilities.
- Record all reported safety events.
- When communicating all safety information to investigators, CRGO and/or HRECs, must clarify the impact of each report on patient safety, trial conduct or trial documentation.
- Must assess and categorise the safety reports received from investigators, and report all suspected unexpected serious adverse reactions occurring in Australian participants to the Therapeutic Goods Administration according to the NHMRC reporting window guidelines for Australian SUSARS. Refer to *NHMRC Safety Monitoring and reporting in clinical trials involving therapeutic goods:*
    - *Appendix 1: Report Flowchart for Investigational Medicinal Product Trials*
    - *Appendix 2: Report Flowchart for Investigational Medicinal Device Trials*
- Must provide updated HREC-approved trial documentation to CRGO as soon as it becomes available, including the annual investigator's brochure update.
- Notify the TGA, HREC and investigators of all significant safety issues that adversely affect the safety of participants or materially impact on the continued ethical acceptability or conduct of the trial as per the NHMRC reporting window guidelines.

The Principal Investigator (PI) or their delegate

- Is responsible for ensuring safety events are assessed, recorded in medical records and reported according to the study protocol and CRGO's policy. Refer to *NHMRC Safety Monitoring and reporting in clinical trials involving therapeutic goods:*
    - *Appendix 1: Report Flowchart for Investigational Medicinal Product Trials*
    - *Appendix 2: Report Flowchart for Investigational Medicinal Device Trials*
- Should provide the sponsor with all relevant information so that an appropriate safety analysis can be performed.
- Should capture and assess all safety events that occur at Cabrini in accordance with the protocol

- Should report to the sponsor any safety events (as defined by the protocol) and USM's instigated at Cabrini to the sponsor within 24 hours of becoming aware of the event;
- Should report any SAEs (refer to the Safety Reporting Summary Table) /SSI and SUSARs arising at Cabrini to the CRGO within 72 hours of becoming aware of the event
- Can delegate trial duties to qualified individuals as long as they possess the requisite training, education and experience to fulfil this role. Delegation must be recorded in the study's delegation and training logs. The PI remains ultimately responsible for any decision made by their delegate.
- Where the assessment of a SUSAR's causality differs between the Sponsor and the PI, the opinions of both the PI and the sponsor should be provided with any SUSAR report sent to the TGA.

Trial Coordination Team

- Facilitates Cabrini's approved requirements for safety monitoring visits
- Ensures monitors meet Cabrini's vaccination requirements and mask mandates
- Is responsible for supporting the PI, AI's and delegated staff in preparing and submitting safety reporting

Cabrini Research Governance Office (CRGO)

- Receives safety reports for any SAE's (refer to the Safety Reporting Summary Table), SSIs and SUSARs occurring at Cabrini, and coordinates review and executive oversight via the Cabrini Research Governance Committee (CRGC).
- Maintains a risk management register of all reportable safety events.

Cabrini Research Governance Committee (CRGC)

- Reviews reportable safety events, incidents and risks occurring at the Cabrini, and determines referral via the organisation's risk management policy
- Supports Academic Research Department Heads:
    - In developing and implementing strategies for risk management in their area of responsibility
    - To inform Executives, via the CRGC, of the high risks and propose risk treatment strategies
    - To escalate risk issues to the Executives, via the CRGC, where appropriate

SAFETY REPORTING POLICY

Cabrini Research endorses and adopts the NHMRC Guidance: Safety monitoring and reporting in clinical trials involving therapeutic goods (2016).

SAEs

Sponsors are required to

- keep detailed records of all reported SAEs and maintain up-to-date tabulations and/or line listings
- assess and categorise the safety reports received from investigators
- Submit any safety related changes to trial documentation to the HREC without undue delay. These HREC-approved amendments must be shared with the investigators to seek CRGO governance approval.

The PI or their delegate is required to:

- capture and assess all SAEs that occur at Cabrini as required (refer to the Safety Reporting Summary Table) and in accordance with the protocol
- report to the sponsor within **24 hours** of becoming aware of the event:
    - all SAEs, except those that are identified in the protocol as not needing immediate reporting
    - any occurrences of congenital anomaly/birth defect arising from any pregnancy of a participant (or partner)
    - all urgent safety measure instigated by the Cabrini PI (or their delegate)
- Share any HREC-approved updated trial documentation resulting from the safety events for CRGO approval.

SUSARs and USADEs

The sponsor is required to report all SUSARs and USADEs occurring in Australian participants to the Therapeutic Goods Administration (TGA)

- for fatal or life threatening Australian SUSARs, immediately, but no later than **7 calendar days** after being made aware of the case, with any follow-up information within a further **8 calendar days**
- for all other Australian SUSARs/USADEs, no later than **15 calendar days** after being made aware of the case

The sponsor must submit any safety related changes to trial documentation to the HREC without undue delay. These HREC-approved amendments must be shared with the investigators to seek CRGO approval. The Principal Investigator is required to report SUSARs/USADEs occurring at Cabrini to the CRGO within **72 hours** of becoming aware of the event. SUSARs occurring at external sites should not be reported to CRGO unless they are deemed by the sponsor to be an SSI.

SSIs and USMs

SSI's usually require other action, such as the reporting of a USM, an amendment, a temporary halt or an early termination of a trial. In addition, SSIs often result in safety-related changes to trial documentation. These amendments should be submitted to the HREC without undue delay. These HREC-approved amendments must be shared with the CRGO for approval.

USMs are one type of SSI where sponsors or trial investigators act immediately to protect participants from an immediate hazard to their health and safety. Consequently, USMs are often instigated before the TGA and HREC are notified. In these cases, it is strongly recommended that the sponsor contact the TGA within **24 hours** of the measure being taken.

The sponsor is required to notify the TGA, HREC and investigators of all significant safety issues that adversely affect the safety of participants or materially impact on the continued ethical acceptability or conduct of the trial for:

- SSI's that meet the definition of a USM should be notified within **72 hours**
- all other significant safety issues should be notified within **15 calendar days** of the sponsor instigating or being made aware of the issue.

The PI or their delegate is required to:

- Report all SSI's to the CRGO within **72 hours** of becoming aware of the event; and

- Report USM's instigated by the site to the sponsor within **24 hours** of becoming aware of the event

AESIs

The PI or their delegate is responsible for determining whether an AESI qualifies for reporting to the CRGO however should ultimately be guided by the reporting requirements of the study protocol. AESIs are not reviewed by HRECs.

CRGO safety reporting guidelines:

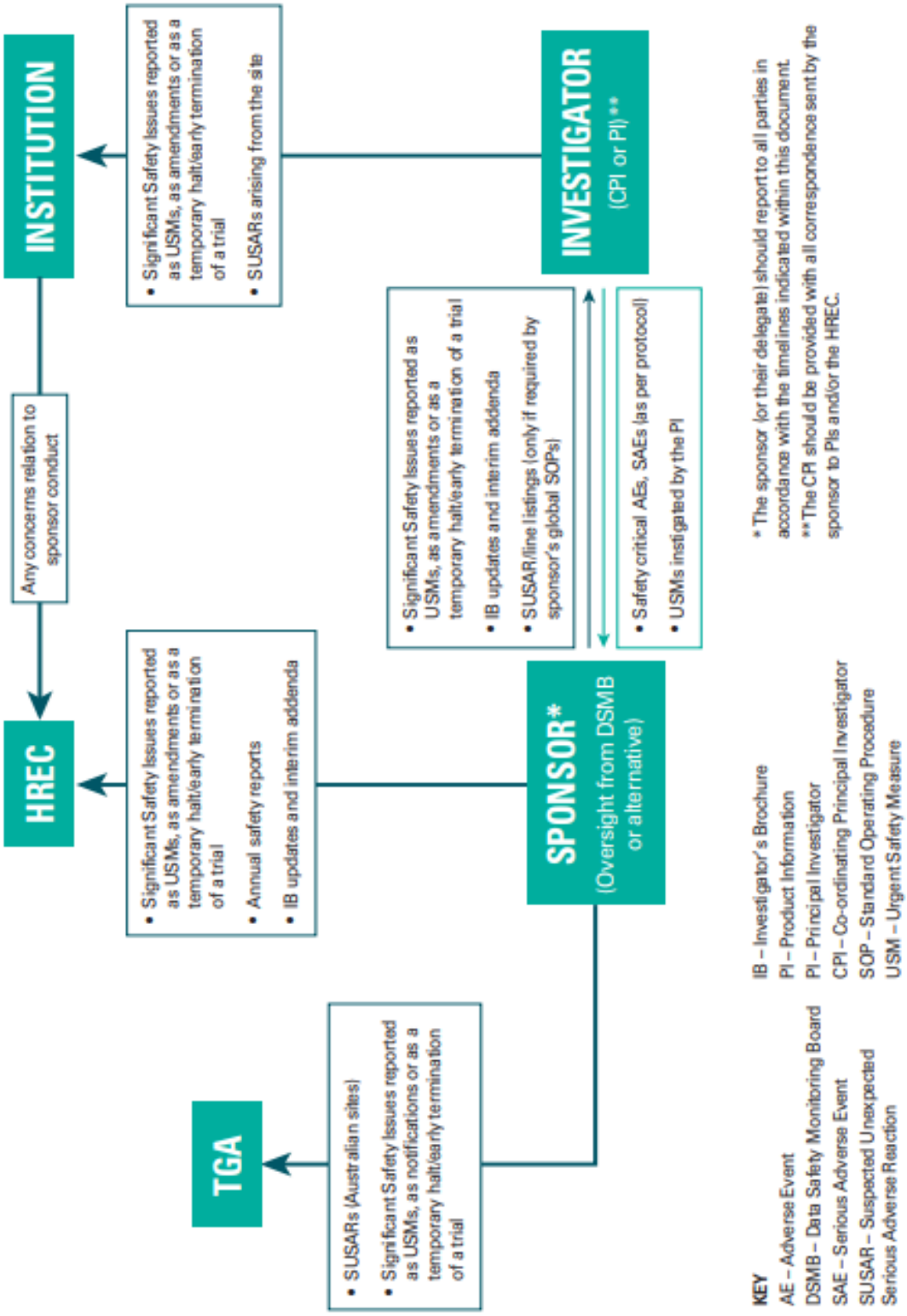
- CRGO will accept the Victorian Government's Safety Report Form (December 2017), Sponsor Safety Report Templates and CIOMS forms. All forms must provide commentary on how the investigator determined the event is related to the investigational product and the health status of the patient at the time of reporting.
- Reports must contain no participant identifiers.
- The PI or their delegate can report any events to the CRGO, the Sponsor or the HREC based on their clinical assessment and opinion, even if the event may not meet the reporting criteria stipulated in the protocol and NHMRC guidance, or if the opinion is not supported by the sponsor.
- Reports are not required by the CRGO if the safety event is not related to the IMP or IMD, or is due to disease progression. If, however, a Cabrini system or process issue has contributed to a clinical trial incident, then reporting is required in Riskman as per Cabrini's Incident Management Policy and Procedures.
- Reportable events must be reported in the Cabrini Research Risk Register.
- An email to researchgovernance@cabrini.com.au to notify the CRGO of a SUSAR, SAE/SSI or USM as soon as it happens in a Cabrini cohort is encouraged.
- If multiple follow-up reports are provided, only those that provide new and useful information that enables meaningful analysis and/or changes perspectives on how the event should be assessed or managed should be presented to the CRGC.
- Development Safety Update Reports (DSURs) executive summaries, line listings, or other periodic safety reports do not require submission to CRGO. The DSUR executive summary can be submitted if the investigator and sponsor feel there is an impact on the conduct of the study.

Safety Reporting Summary Table (*Calendar Days)

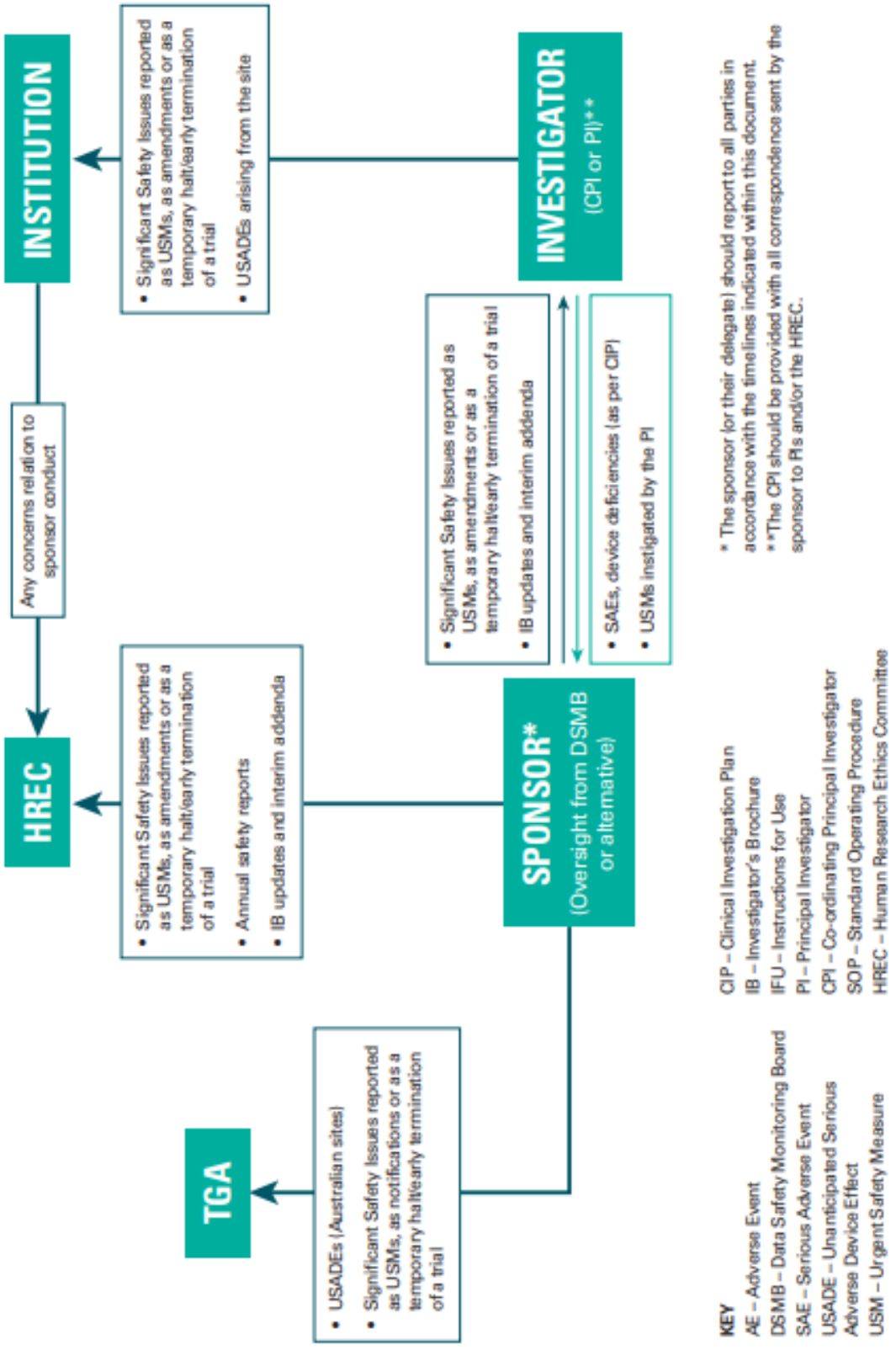
Event	Resp.	Action	Reporting Window	Tool
SAE, SADE	Sponsor	• keep records of all reported events • maintain up-to-date tabulations / line listings • assess and categorise the safety reports from PIs	N/A	N/A
	PI or delegate	Capture and assess all Cabrini events in accordance with the protocol and report to the sponsor: • all events the protocol mandates for immediate reporting • occurrences of congenital anomaly/birth defect arising from any pregnancy of a participant (or partner) • all urgent safety measure instigated by the Cabrini PI Report all Cabrini SUSARs / USADEs to CRGO i.e. safety events that are both unexpected, serious and related (or suspected as being related) to the IMP/IMD. Disease progression is not reportable to CRGO.	Within 24hrs of becoming aware of event Within 72hrs of becoming aware of event	Vic Govt safety / sponsor / CIOMS forms
SUSARs USADEs	Sponsor	Report Australian events to the TGA • fatal or life-threatening Australian events • for all other Australian events	Immediately, but no more than 7* days after becoming aware of event, follow-up info within a further 8*days no more than 15* days after becoming aware of event	Refer to TGA sponsor regulatory reporting requirements page
	PI or delegate	Report Cabrini events to the CRGO Report external (non-Cabrini) events only if they have been deemed by the sponsor to be an SSI.	Within 72hrs of becoming aware of the event. Within 72hrs of becoming aware of the event.	Vic Govt safety / sponsor / CIOMS forms
SSI, USM	Sponsor	• Alert the TGA of any USMs *instigated before the TGA and HREC were notified* • Notify the TGA, HREC and PIs of SSI's that meet the definition of a USM • Notify the TGA, HREC and PIs of all other significant safety issues	Within 24hrs of the measure being taken Within 72hrs of becoming aware of the issue Within 15* days of instigating or becoming aware of the issue	Refer to TGA sponsor regulatory reporting requirements page

	PI or delegate	• Report all SSI's to the CRGO • Report USM's instigated by the Cabrini PI to the sponsor and CRGO	Within 72hrs of becoming aware of the event Within 24hrs of becoming aware of the event	Vic Govt safety / sponsor / CIOMS forms
AESI	PI or delegate	• Report to sponsor as per protocol. • Report to CRGO if the PI deems it necessary.	As per protocol PI's judgement	Sponsor form

Appendix 1: Report Flowchart for Investigational Medicinal Product Trials



Appendix 2: Reporting Flowchart for Investigational Medical Device Trials



REQUIREMENTS
Victorian State Government Safety Report Form

REVIEW
This policy should be reviewed every 3 years or sooner if in response to national and state regulatory changes. Non-material amendments may be proposed at any time and approved by the Group Director Research.

REFERENCES and ASSOCIATED DOCUMENTS
Integrated Addendum to ICH E6(R1): Guideline for Good Clinical Practice ICH E6(R2)
NHMRC Safety monitoring and reporting in clinical trials involving therapeutic goods
Clinical Incident Management Policy and Procedures
Risk Management

Key Legislation and Standards
National Clinical Trials Governance Framework

ACKNOWLEDGEMENTS
Monash Health Research Ethics and Governance Safety Reporting Procedure
Epworth Management and Reporting of Safety Events
Alfred Health Safety Monitoring & Reporting

REVISION HISTORY

Version	Revision date	Revision notes
1.0	1 September 2023	New document
1.1	4 April 2024	**Safety Reporting Summary Table – SAE/SADE:** replace reporting of all grade 3+ severity events related to IMP/IMD with SUSARs/USADES to safety events that are unexpected, serious and related to the IMP/IMD (greater alignment with NHMRC guidance) **Riskman Reporting Criteria:** when **a Cabrini system or process issue has contributed to a clinical trial incident**

Executive Sponsor	**Group Director Cabrini Research**	
Approved By:	Cabrini Research Governance Committee	**Date: 3 August 2023**
Authorised By:	Clinical Policy Committee Group Director Cabrini Research	**Date:** 1 September 2023 **Updated:** 12 April 2024