CLINICAL TRIALS - SAFETY REPORTING

PROCEDURE ©

DOCUMENT SUMMARY/KEY POINTS

- This procedure:
  - Provides guidance about safety reporting requirements to researchers conducting research at SCHN
  - Aligns with the NHMRC National Statement on Ethical Conduct in Human Research (2007 and updates) and the NHMRC Safety Monitoring and Reporting in Clinical Trials involving Therapeutic Goods (November 2016 and updates)
  - Aligns with NSQHS National Standard 1: Clinical Governance

CHANGE SUMMARY

- Not applicable – new document.

READ ACKNOWLEDGEMENT

- Read Acknowledge Only – All SCHN staff involved in the conduct of clinical research

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Purpose/Scope

This document outlines the procedures and requirements for reporting safety events in clinical trials. This procedure covers clinical trials that involve the use of an investigational medicinal product (IMP), investigational biologicals, or investigational medical devices (IMDs) that are conducted under the Clinical Trial Notification (CTN) or Clinical Trials Approval (CTA) Scheme as well as other non-interventional trials where safety issues may occur (eg surgical, psychotherapy, radiotherapy trials).

Safety events includes adverse events (AEs), serious adverse events (SAEs), adverse events of special interest (AESI), suspected unexpected serious adverse reactions (SUSARs), Unanticipated Serious Adverse Device Effect (USADEs) or significant safety incidents (SSIs).

This procedure applies to all SCHN employees, including contingent workers and visiting medical officers (VMOs) involved in research and to all relevant external persons or parties engaged in research at SCHN.

This procedure aligns with the National Safety Quality Health Service (NSQHS) Standard 1: Clinical Governance, actions 1.3, 1.5, 1.6 and 1.7.

Expected Results

Adherence to this procedure will facilitate appropriate monitoring, reviewing, and monitoring documentation of safety events that occur during clinical trials and appropriate reporting of safety events to the approving Human Research Ethics Committee (HREC), SCHN Research Governance Office (RGO), clinical trial sponsors and the Therapeutic Goods Administration (TGA).

Responsibilities

Sponsor Responsibilities

The NHMRC Safety Monitoring and Reporting in Clinical Trial involving Therapeutic Goods Guidelines (November 2016) provides guidance of sponsor responsibilities for clinical trials.

Clinical trial sponsors are responsible for the ongoing safety evaluation of their trials. Sponsors can delegate some or all sponsor functions to other individuals or third parties, such as the Coordinating Principal Investigator (CPI), a Data Safety Monitoring Board (DSMB), a clinical research organisation (CRO), or a coordinating centre.

Where the sponsor is SCHN, the responsibility of safety reporting is delegated to the CPI. Where the CPI is also the site PI, they will undertake both sponsor and investigator responsibilities as detailed in this document.

For multi-centre research, the CPI is responsible for reviewing all safety events reported by members of the lead site research team and Investigators from participating sites. The Principal Investigator (PI) at each site is responsible for local safety monitoring and reporting.

The CPI and site PIs are responsible for supervising any individual to whom they have delegated safety monitoring or reporting duties.

Investigator Responsibilities

Investigators are responsible for the ongoing reporting of safety events that occur in research participants at their site throughout the life of the trial. They must have the necessary training and experience to undertake their ICH-GCP responsibilities for safety monitoring and reporting.

Human Research Ethics Committee (HREC) Responsibilities

Human Research Ethics Committees are responsible for evaluating the risk-benefit ratio of research being conducted under their approval, ensuring that safety monitoring plans outlined in the protocol are appropriate, ensuring that participants are informed about the risks and benefits of research participation, and acknowledging receipt of any safety-related communication.

Research Governance Office (RGO) Responsibilities

Research Governance Offices must maintain oversight of any significant safety incidents (SSIs) that occur at the institution. This includes Urgent Safety Measures (USMs), SUSARs or USADEs, or any clinical incidents that occur in accordance with NSW Policy Directive PD2020_047 Incident Management.

The RGO is responsible for ensuring that appropriate processes are in place to minimise any risks to the participant and the institution.

Abbreviations and definitions

AE	Adverse Event
AESI	Adverse Event of Special Interest
CPI	Coordinating Principal Investigator
CTA	Clinical Trial Approval
CTN	Clinical Trial Notification
HREC	Human Research Ethics Committee
ICH-GCP	International Council for Harmonisation Guideline for Good Clinical Practice
IMD	Investigational Medical Device
IMP	Investigational Medicinal Product
Interventional clinical trial	A clinical trial investigating the safety and/or effectiveness of medicines, biologicals or medical devices
NHMRC	National Health and Medical Research Council
Non-interventional clinical trial	A clinical trial that does not involve the use of a therapeutic good (eg radiotherapy, surgery, psychotherapy trials)

PI	Principal Investigator
REGIS	Research Ethics and Governance Information System
RGO	Research Governance Office
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SCHN	Sydney Children's Hospitals Network
SSI	Significant Safety Issue
SUSAR	Serious Unexpected Suspected Adverse Reaction
TGA	Therapeutic Goods Administration
URSAE	Unexpected and Related Serious Adverse Event
USADE	Unanticipated Serious Adverse Device Effect
USM	Urgent Safety Measure

Related Documents

1. SCHN Policy – Research Policy – DRAFT
2. SCHN Policy – Research Integrity – DRAFT
3. SCHN Procedure – Research Governance – DRAFT
4. SCHN Procedure – Clinical Trial Sponsorship – DRAFT
5. SCHN Procedure - Research Data Management – DRAFT
6. The National Statement on Ethical Conduct in Human Research (2007) (National Statement (2007), and as updated
7. NHMRC Guidance: Safety Monitoring and Reporting in Clinical Trials Involving Therapeutic Goods (November 2016)
8. NSWH Policy Directive: Safety Monitoring and Reporting for Clinical Trials Conducted in NSW Public Health Organisations PD2017_039
9. NSWH Policy Directive: Incident Management PD2020_047

Procedure

There are four bodies that receive safety reporting communication from a clinical trial:

- Human Research Ethics Committee (HRECs)
- Research Governance Office (RGO)
- Sponsors
- Therapeutic Goods Administration (TGA)

1 HREC Reporting Requirements

Human Research Ethics Committees (HRECs) are responsible for reviewing the overall risk-benefit ratio of clinical trials being conducted under their approval.

For clinical trials that are approved at more than one site under the one Ethics approval, the Sponsor/Coordinating Principal Investigator (CPI) is responsible for reporting safety events and information to the lead HREC.

If the clinical trial is approved at a single site under the one Ethics approval, the Sponsor/Site Principal Investigator of that site is responsible for reporting to HREC.

The process for reporting will vary depending on whether the HREC is in NSW/ACT or not.

Safety reporting in clinical trials approved by HRECs in NSW/ACT is completed via REGIS (REGIS Quick Reference Guide). For those trials approved by HRECs outside of REGIS, the CPI is to follow the approving HREC processes.

The table below lists what safety information must be reported to HRECs.

Event Type	Reporting responsibility (SCHN is Sponsor)	Reporting responsibility (SCHN is not Sponsor)	Timeframe	NSW/ACT HREC	Not NSW/ACT HREC
Significant Safety Issue (SSI) that leads to the implementation of an Urgent Safety Measure (USM)	CPI reports to lead HREC	Sponsor sends to CPI CPI reports to lead HREC	≤ 72 hours after becoming aware of the event	SSI notification form in REGIS **'New form' > 'Significant Safety Issue Notification'** form. Complete REGIS form and upload relevant documents	As per the HREC processes
All other SSIs	CPI reports to lead HREC	Sponsor sends to CPI CPI reports to lead HREC	≤ 15 days after becoming aware of the event	SSI notification form in REGIS **'New form' > 'Significant Safety Issue**	

				Notification' form. Complete REGIS form and upload relevant documents	
If the study is ceased due to safety or futility reason	CPI reports to lead HREC	Sponsor sends to CPI CPI reports to lead HREC	≤ 15 days after becoming aware of the event	SSI notification form in REGIS **'New form' > 'Significant Safety Issue Notification'** form. Report type = **'Early Termination of a Trial for Safety Reasons'** Complete REGIS form and upload relevant documents	
If the study is temporarily halted due to a safety reason	CPI reports to lead HREC	Sponsor sends to CPI CPI reports to lead HREC	≤ 15 days after becoming aware of the event	SSI notification form in REGIS **'New form' > 'Significant Safety Issue Notification'** form. Report type = **'Temporary Halt of a Trial for Safety Reasons'** Complete REGIS form and upload relevant documents	As per the HREC processes
Annual Safety report	CPI reports to lead HREC	Sponsor sends to CPI CPI distributes to site PIs CPI reports to lead HREC on behalf of all sites	Annually	Submitted with the annual progress report via REGIS Click on the **'Milestone'** tab within the ethics application in REGIS and attach the report	
IB updates/addenda	CPI reports to lead HREC	Sponsor sends to CPI CPI distributes to site PIs	As received/ updated	Submitted as amendment in REGIS	

		CPI reports to lead HREC on behalf of all sites			

2 RGO Reporting Requirements

Research Governance Offices (RGOs) are required to monitor the safety of a clinical trial conducted at their institution and ensure that appropriate processes are in place to minimise any risks to the participant and the institution.

RGOs must receive communications about safety events that occur at the institution and where appropriate act on this information to ensure any potential impacts on the individual and institution are minimised.

Important: Any significant safety event that occurs in a SCHN participant or significantly impacts the conduct of the study at SCHN should be reported to RGO as soon as possible.

Investigators are responsible for assessing the seriousness, causality, and expectedness of an adverse event to the trial intervention. If it is not possible to rule out a relationship to the trial intervention, the investigator must report the event to RGO as a SUSAR/USADE.

The table below lists what safety information must be reported to RGOs.

Event Type	Reporting responsibility	Timeframe	NSW/ACT HREC	Not NSW/ACT HREC
Significant Safety Issue (SSI) that meets the definition of an Urgent Safety Measure (USM)	Site PI	≤ 72 hours after becoming aware of the event	Site PI to complete SSI notification form and submit to SCHN-Governance@health.nsw.gov.au *Sponsor/CPI will distribute this information to site PIs.* *These events should be reported to RGO by site PI within the timeframes specified. Site PI should not wait until HREC has approved/acknowledged these events.*	
All other SSIs	Site PI	If occurred at SCHN: ≤ 72 hours after becoming aware of the event If occurred outside of SCHN: ≤ 15 days after becoming aware of the event		
If the study is ceased due to safety or futility reason	Site PI			
If the study is temporarily halted due to a safety reason	Site PI			

Any SAE that meets criteria for SUSAR or USADE – SCHN participants only	Site PI	≤ 72 hours after becoming aware of the event	Site PI to complete SUSAR-USADE-URSAE Notification form and submit to SCHN-Governance@health.nsw.gov.au *Site PI should not wait for Sponsor assessment of SAE/SUSAR before reporting to RGO*	
Annual Safety report	Site PI	Annually	Submitted with the annual progress report by CPI to HREC via REGIS Once approved by HREC, automatically forwarded to RGOs Nothing for site PI to action Site PI will not receive RGO approval/acknowledgement	Site PI (or delegate) to request RGO to create an annual progress report milestone in REGIS STE application > Milestone > Annual Progress Report Complete form on REGIS and attach safety report and related documents Site PI will not receive RGO approval/acknowledgement
IB updates/addenda	Not required to be submitted to RGO			

Some protocols will list specific adverse events of special interest (AESI), AEs/Lab Evaluations (critical to safety), AEs and device deficiencies and pregnancies with different sponsor reporting requirements. Site PIs are to follow the reporting timelines as provided in the protocol.

3 Sponsor Reporting Requirements

Sponsors ensure that each investigator is trained and experienced to undertake the safety reporting responsibilities as per ICH-GCP. The safety and welfare of individual research participants is the responsibility of the Principal Investigator at each institution.

The Sponsor is responsible for the dissemination of trial safety communications as per the NHMRC Safety Monitoring and Reporting in Clinical Trials involving Therapeutic Goods Guidelines or as described in the protocol.

Investigators are responsible for reporting any adverse event as stated in the protocol. Should RGO request the implementation of an urgent safety measure as a result of an adverse event, the investigator must report this to the trial sponsor as soon as possible.

The table below lists what safety information must be reported to Sponsors.

Event Type	Reporting responsibility (SCHN is Sponsor)	Reporting responsibility (SCHN is not Sponsor)	Timeframe
Safety critical AEs, SAEs, device deficiencies (as per protocol)	CPI/PI reports to SCHN-Governance@health.nsw.gov.au	CPI/PI reports to Sponsor	As soon as possible and between ≤24 to 48 hours after becoming aware of the event or as stated in protocol
Urgent safety measures instigated by the site	CPI/PI reports to SCHN-Governance@health.nsw.gov.au via SSI notification form		As soon as possible and between ≤72 hours after becoming aware of the event

4 TGA Reporting Requirements (Interventional Clinical Trials Only)

An interventional clinical trial is a research project which investigates the safety and/or effectiveness of medicines, biologicals or medical devices. Clinical trial sponsors are responsible for reporting any significant safety events that occur in a trial involving the use of therapeutic goods to the Therapeutic Goods Administration (TGA).

Safety events that occur in a non-interventional research project are not required to be submitted to the TGA. A non-interventional clinical trial is a research project which does not involve the use of a therapeutic good. Examples of non-interventional clinical trials include radiotherapy, surgery and psychotherapy trials.

The table below lists what safety information must be reported to the TGA.

<table>
<tr><th>Event Type</th><th>Reporting responsibility (SCHN is Sponsor)</th><th>Reporting responsibility (SCHN is not Sponsor)</th><th>Timeframe</th></tr>
<tr><td>Serious Adverse Events that occur in Australia</td><td>CPI/SCHN reports to TGA via Blue card/CIOMS form

Email: adr.reports@health.gov.au

Online via TGA Business Services</td><td>CPI/PI reports to Sponsor

Sponsor reports to TGA via Blue card/CIOMS form

Email: adr.reports@health.gov.au

Online via TGA Business Services</td><td>≤ 15 days after receipt of minimum information</td></tr>
<tr><td>SSIs reported as USMs, temporary halt or early termination of the trial</td><td rowspan="2">CPI/SCHN reports to TGA in writing to PSAB Signal Investigation Coordinator:

si.coordinator@health.gov.au</td><td rowspan="2">CPI/PI reports to Sponsor

Sponsor reports to TGA in writing to PSAB Signal Investigation Coordinator:

si.coordinator@health.gov.au</td><td>≤72 hours after becoming aware of the event</td></tr>
<tr><td>A SUSAR in an Australian trial participant that represents a serious threat to public health</td><td>≤ 48 hours after becoming aware of the event</td></tr>
</table>

A SUSAR in an Australian trial participant that leads to death or a serious deterioration in the state of health of a patient, a user of the device or another person			≤ 10 days after becoming aware of the event
A SUSAR in an Australian trial participant that ***might*** lead to the death or a serious deterioration in the state of health of a patient, a user of the device or another person			≤ 30 days after becoming aware of the event

Bibliography

SCHN References

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- The Sydney Children's Hospitals Network [Internet]. Research; Ethics | Governance; Research Governance. Safety reporting. [Accessed 22.06.2023]. Available from: (https://www.schn.health.nsw.gov.au/research/ethics-governance/research-governance/safety-reporting)
- SCHN Forms
  - SCHN RGO SSI Notification Form (https://www.schn.health.nsw.gov.au/files/attachments/ssi_notification_form.pdf)
  - SCHN RGO SUSAR-USADE-URSAE Notification Form (https://www.schn.health.nsw.gov.au/files/attachments/susar_notification_form.pdf)

External References

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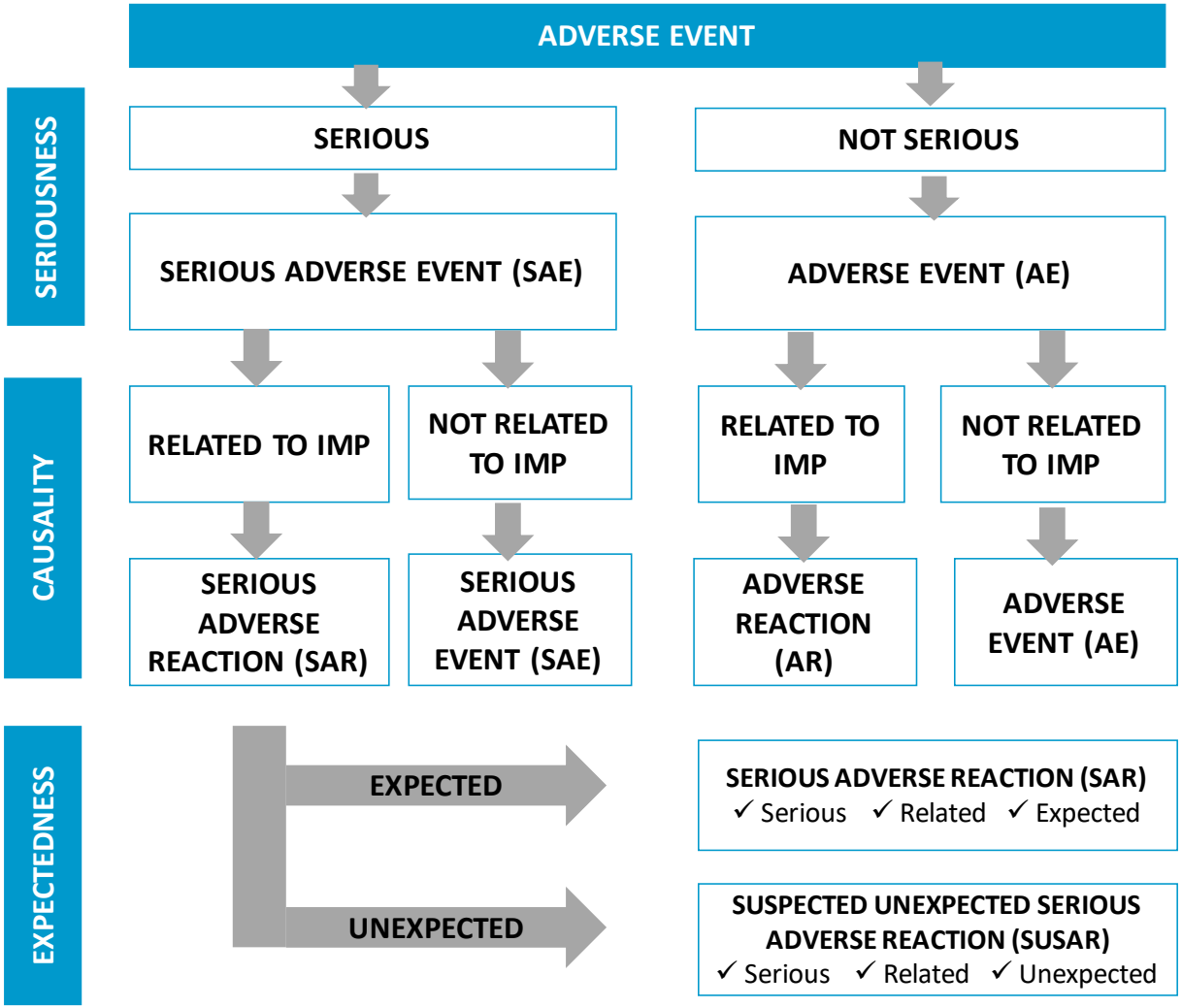
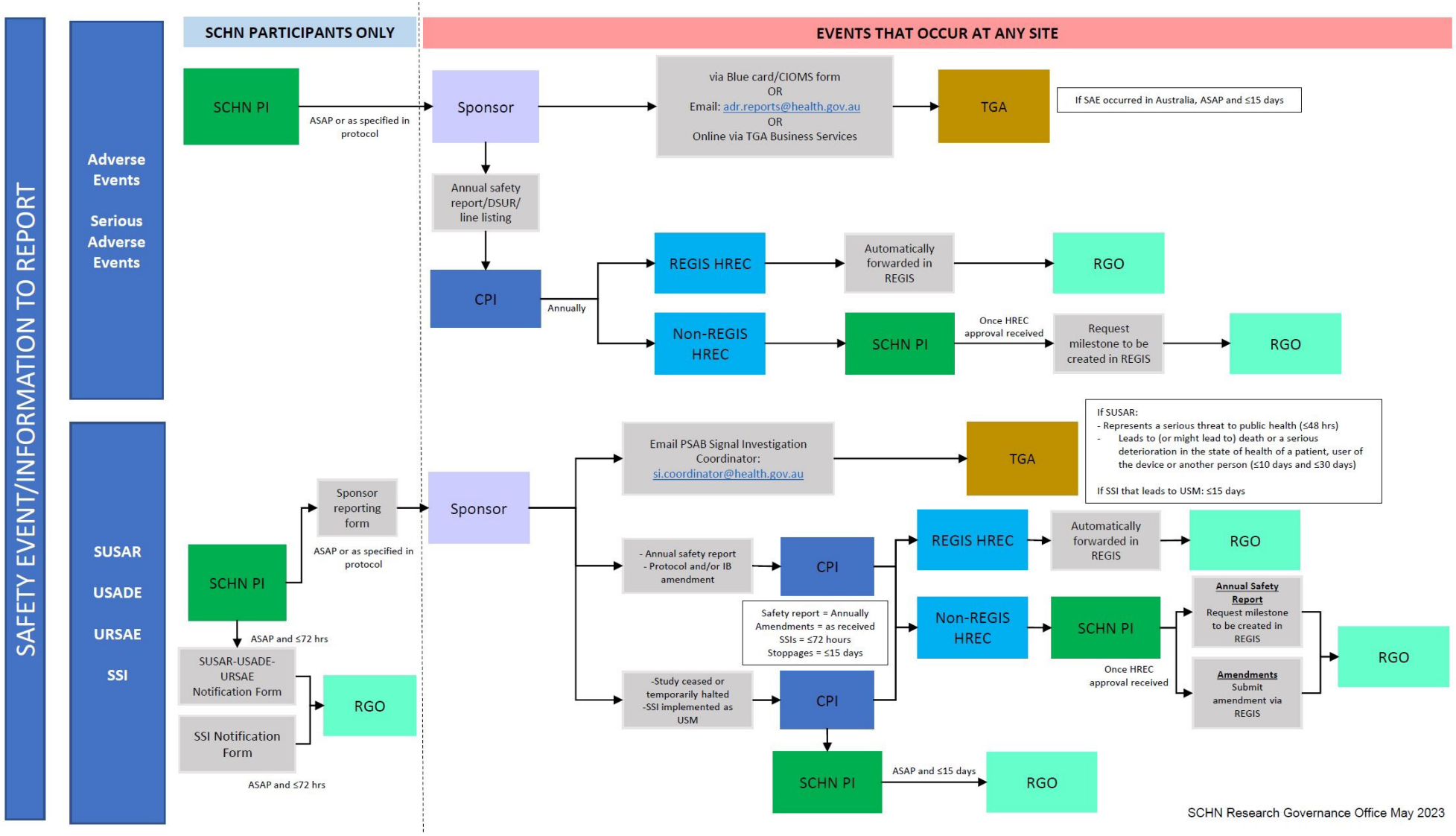
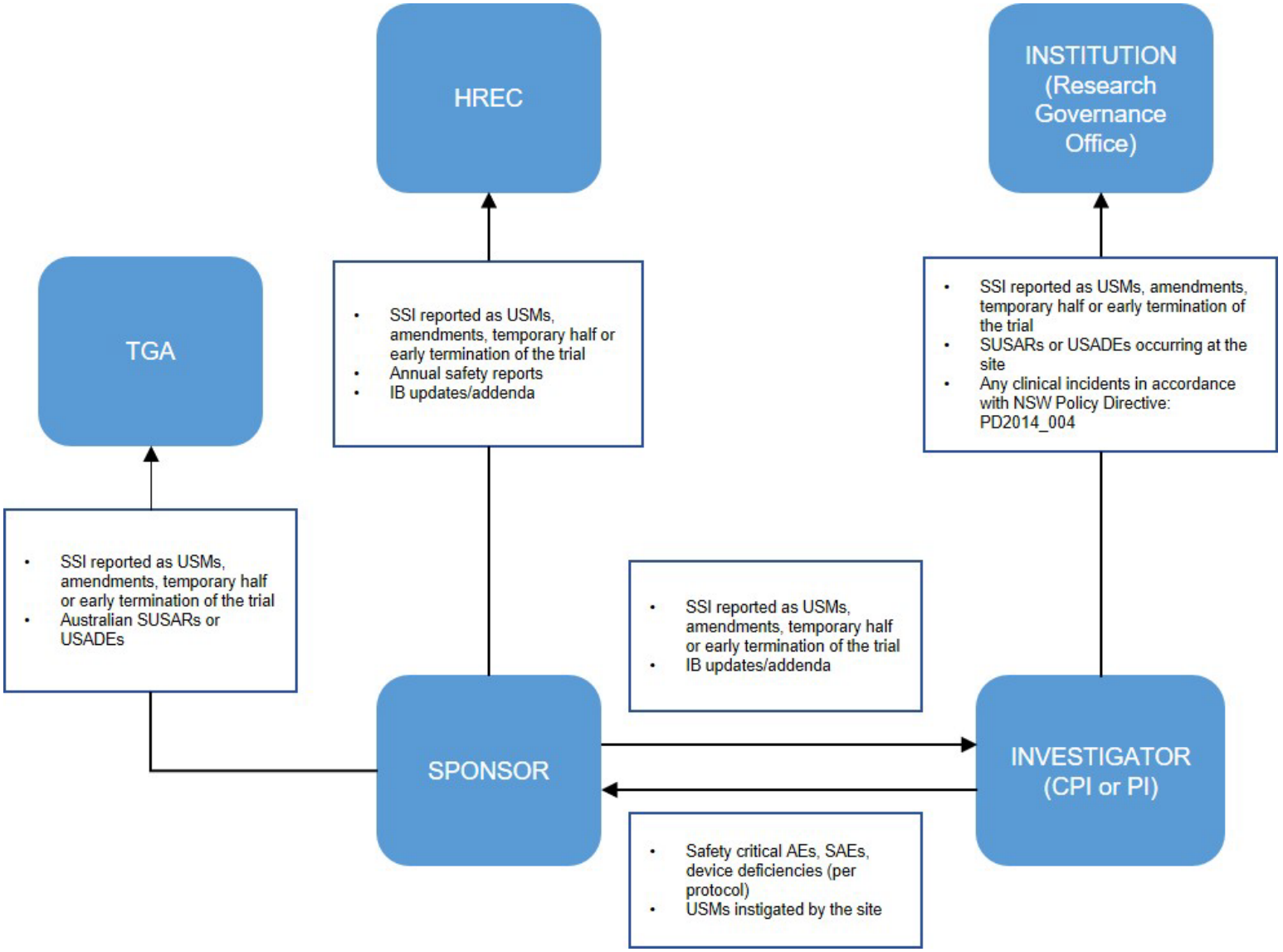
APPENDIX I: Safety Reporting Assessment Flowchart for Interventional Clinical Trials



APPENDIX II: Safety Reporting Flowchart for SCHN Clinical Trials



APPENDIX III: Safety Reporting Flowchart for Interventional Trials



APPENDIX IV: Safety Reporting Flowchart for Non-Interventional Clinical Trials