

Safety Monitoring & Reporting of Research Projects Procedure

Purpose:

The purpose of this document is to provide researchers and research teams with guidance about the monitoring and safety reporting requirements which may occur during the time of their research project.

This document describes the procedures for:

1. monitoring research projects approved by the Eye and Ear Human Research Ethics Committee (HREC)
2. monitoring research projects granted Research Governance Authorisation by the Eye and Ear under Streamlining procedures
3. the reporting and handling of Serious Adverse Events (SAE) and other adverse events
4. the reporting and handling of Serious Breaches of Good Clinical Practice (GCP) or the Protocol.

Scope:

This procedure applies to all research approved by the Eye and Ear HREC and all research conducted by and at the Eye and Ear authorised by the Eye and Ear Research Office approved by a third-party HREC, , including clinical trials or investigations involving medicines, devices and/or biologicals.

This procedure is applicable to principal investigators, organisations and sponsors, whether the research is commercially sponsored or otherwise. Where there is delegation of sponsor functions, the responsibility extends to that third party.

Risks/Precautions:

None have been identified at the time of this review.

Principles for Safety Monitoring and Reporting:

1. The Eye and Ear applies a risk-based approach to monitoring of all research which is in accordance with the (NHMRC)'s *National Statement on Ethical Conduct in Human Research* (National Health and Medical Research Council (NHMRC) 2023 and as amended).
2. Monitoring arrangements should be commensurate with the risk, size and complexity of the research (National Statement 2023, 5.4.2).

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3. Risk Assessment can be conducted using any model. Suggested models include:
 - Using Table 1 and Table 3 of the NHMRC guidelines¹
 - Using other tools available for risk assessment such as:
 - European Clinical Research Infrastructure Network (ECRIN)

<https://www.ecriin.org/tools/risk-based-monitoring-toolbox>
4. Responsibility for ensuring that research is reliably monitored lies with the institution under which the research is conducted (*National Statement 2023*, 5.4.1).
5. All research projects approved by the Eye and Ear HREC irrespective of whether the Eye and Ear is an investigational site, will be monitored according to the procedures in Section B.
6. Where projects are conducted at the Eye and Ear and have been approved by a HREC institutionally certified by the NHMRC for multi-centre research (National Certification Scheme), the safety monitoring and reporting requirements of the reviewing HREC and of the Eye and Ear must both be followed.
7. All information related to monitoring and safety reporting at the Eye and Ear is available:
 - On the Eye and Ear Research Office website – for all information and forms
 - On Riskman – must have access to the Eye and Ear Intranet
8. Principles specific to clinical trials
 1. The Eye and Ear Hospital adopts the following guidelines:
 - NHMRC Guidance: Safety monitoring and reporting in clinical trials involving therapeutic goods (NHMRC; November 2016)
 - NHMRC Guidance Risk-based Management and Monitoring of Clinical Trials involving Therapeutic Goods (NHMRC; 2018)
 - NHMRC Guidance Reporting of Serious Breaches of Good Clinical Practice (GCP) or the Protocol for Trials Involving Therapeutic Goods (NHMRC; 2018)
 - NHMRC Guidance Data Safety Monitoring Boards (DSMBs) (NHMRC; 2018)
9. Every clinical trial must have a designated Sponsor

¹ Risk-based Management and Monitoring of Clinical Trials Involving Therapeutic Goods NHMRC 2018

10. Sponsors must undertake all responsibilities as outlined in the guidance documents referred to in point 8(1).
11. All Clinical Trials must have one or more of the following
 - a. Independent committee (i.e., Data Safety Monitoring Board); or
 - b. Independent individual (i.e., Medical Monitor); or
 - c. Other mechanism for monitoring; or
 - d. Justification for not having any of a – c above.
12. Research teams, Research Partners, and other organisations conducting research projects at the Eye and Ear and/or involving Eye and Ear patients are responsible for ensuring trials are designed, managed and monitored appropriately.

Procedure / Method:

The following sections outline the safety monitoring and reporting requirements at each stage of the research approval process.

Section A: Monitoring

For the duration of an approved research project, the Reviewing HREC is responsible for monitoring the ethical conduct and safety of the research. The Reviewing HREC monitors approved projects to ensure compliance with the Committee's own conditions, the research protocol, the National Statement and relevant legislation and guidelines. Failure to comply with these safety monitoring requirements may result in the Reviewing HREC suspending or withdrawing its approval for the research.

If the Eye and Ear HREC is the Reviewing HREC then all reports must be submitted to the Eye and Ear HREC. If another HREC is the Reviewing HREC and the Eye and Ear is an investigational site and has issued Research Governance Authorisation, the reports must be submitted to both the Reviewing HREC, according to their requirements, and to the Eye and Ear Research Office.

The mechanisms for monitoring research projects at the Eye and Ear are detailed below:

1. Annual Reports and Self Audit

Each Annual Progress Report must include a Self-Audit Report which must be submitted to the Eye and Ear Research Office by the Principal Investigator (PI) (or their delegate).

The Eye and Ear Research Office identifies annual report / self-audit due dates and advises the PI of this.

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The Annual Progress Report should be submitted on the annual report/self-audit form which is available on the Eye and Ear Research Office website. The annual report is reviewed at the HREC meeting just prior to the anniversary of the Eye and Ear HREC approval date (or renewal date). The self-audit report is reviewed by the HREC Secretary and any issues of concern are forwarded to the HREC Chair for resolution or review by the HREC if deemed appropriate by the Chair.

Any queries, comments or clarifications raised by the HREC are to be sent to the PI by the Ethics Secretary within 10 working days of the HREC meeting.

If no queries are raised, the Annual Report / Self-Audit is (are) accepted and ethical approval is continued and the PI is advised of this by the HREC Secretary.

2. **Final Reports**

A final report must be submitted to the Research Office by the PI (or their delegate) at the completion of a research project or if the project has been discontinued.

The Research Office identifies final report due dates and advises the PIs regarding this. The final report should be submitted on the 'Final Report Form' which is available via the Research Office webpages.

The final report will be included in the agenda papers at the next HREC meeting. The HREC reviews the report and any queries raised are sent to the PI for clarification by the HREC Secretary within 10 working days of the HREC meeting. If no queries are raised, the final report is accepted and the PI is advised of this.

3. **Planned or random audits**

The Research Office may conduct a planned or random audit on any aspect of the research project. The audit may be conducted by an internal or external individual with the appropriate expertise related to the research project. The PI will be notified that an audit will occur, by whom and the time frame.

4. **Other progress reports**

The Eye and Ear HREC may require additional progress reports to be submitted for projects that are deemed to be high-risk or for which there are multiple reportable events. The requirement for additional progress reporting is at the discretion of the HREC. When required, information about the report format and reporting time frames will be communicated to the PI, in writing, by the HREC Secretary.

5. **Suspension or Withdrawal of Ethical Approval**

There are number of reasons why ethical approval of a research project may be suspended by the HREC. These include:

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- Failure to supply a completed Annual or Final Report
- If the conduct of a research project is found to be non-compliant with the HREC's conditions of approval
- Any concerns raised regarding the safety of the project

Most seriously, a project's approval may also be withdrawn if there are participant welfare and safety concerns.

If the HREC makes a decision to suspend or withdraw approval for a research project, this decision is conveyed in writing by the HREC Chair to the PI. This includes details of the reason/s for the suspension/withdrawal, will highlight where the research was inconsistent with the principles of the National Statement, and will include a statement that the research project must be suspended or cease. It will also provide advice on what needs to be rectified for ethical approval to be reinstated.

Refer to Procedure RS 1.5 Suspension or Withdrawal of Approval for Conduct of Research Projects

6. Reinstatement of Ethical Approval

If a research project has been suspended by the Eye and Ear HREC, the PI can request reinstatement of ethical approval by the HREC. The HREC will consider the information provided by the PI and evaluate whether it is satisfied that the welfare and safety of research participants has been addressed. This may involve the PI submitting a list of amendments to be made to the research project for the HREC's consideration.

The HREC Secretary will advise the PI, in writing, of the outcome of the request for reinstatement. Research cannot recommence until the HREC is satisfied, has re-approved the project, and the PI has been formally advised.

Refer to Procedure RS 1.5 Suspension or Withdrawal of Approval for Conduct of Research Projects

Section B: Deviations or Violations of the Protocol / project description and Non-Serious Breaches and Serious Breaches

1. Non-clinical Research Projects and Clinical Research Projects

1. Deviations or Violations of the Protocol/project description

1. Procedure for research projects granted ethical approval by the Eye and Ear HREC

All research project deviations or violations involving the Eye and Ear must be reported:

- to the Eye and Ear Research Office
 - as soon as possible and within 72 hours of occurrence
 - using the [EAE Protocol Deviation or Violation Reporting Form](#)
2. Procedure for research projects granted ethical approval by another Reviewing HREC and granted Research Governance Authorisation by the Eye and Ear:

All research project deviations or violations involving the Eye and Ear must be reported:

- to the Eye and Ear Research Office
- as soon as possible and within 72 hours of occurrence
- using the [EAE Protocol Deviation or Violation Reporting Form](#)
- to the Reviewing HREC as required by the Reviewing HREC
- If submitted to the Reviewing HREC then submit Reviewing HREC response to the Eye and Ear Research Office

2. **Clinical Trials**

Principal Investigators must report all Non-serious or Serious Breaches of Good Clinical Practice and the Clinical Trial Protocol to the Sponsor.

1. Non-serious Breaches

1. Procedure for research projects granted ethical approval by the Eye and Ear HREC

Non-Serious Breaches must be reported:

- to the Eye and Ear Research Office
- as soon as possible and within 7 days

- using the Non-Serious Breach – Deviation Report Form [DHHS supplied] as instructed on the Research Office website.
2. Procedure for research projects granted ethical approval by another Reviewing HREC and granted Research Governance Authorisation by the Eye and Ear .

All Non-serious Breaches involving the Eye and Ear must be reported

- as above in B.2.1.1; and
- to the Reviewing HREC as required by the Reviewing HREC
- If submitted to the Reviewing HREC then submit HREC response to the Eye and Ear Research Office

2. **Serious Breaches**

1. Procedure for research projects granted ethical approval by the Eye and Ear HREC

Serious Breaches must be reported:

- to the Eye and Ear Research Office
 - as soon as possible and within 72 hours
 - using the Serious Breach Report Form (Sponsor) [DHHS supplied] as instructed on the Research Office website.
2. Procedure for research projects granted ethical approval by another Reviewing HREC and granted Research Governance Authorisation by the Eye and Ear

All Serious Breaches involving the Eye and Ear must be reported:

- as above in B.2.2.1; and
 - to the Reviewing HREC as required by the Reviewing HREC
 - If submitted to the Reviewing HREC then submit HREC response to the Eye and Ear Research Office
3. Suspected Breaches

A third party (e.g., individual/institution) can report a suspected breach of Good Clinical Practice or the protocol directly to the Reviewing HREC without reporting through the Sponsor.

Submit the Suspected Breach Report Form (Third Party) [DHHS supplied] as instructed on the Research Office website.

Section C: Adverse Events and Safety Reporting

Clinical research

Roles and responsibilities

Firstly, for all adverse events, the members of the research team are responsible for managing and treating the clinical situation to ensure the research participant's safety, health and well-being. Secondly, Principal Investigator must capture and assess all Adverse Events (AEs) in accordance with the Study Protocol / project description.

Procedures

1. Procedure for research projects granted ethical approval by the Eye and Ear HREC
 1. All **Adverse Events** that occur as part of a research project must be reported to the Eye and Ear Research Office.
 1. The report must be submitted:
 - a. to Eye and Ear Research Office
 - b. as soon as possible and within 72 hours of occurrence
 - c. using the EAE Single Adverse Event Report Form
 2. Procedure for research projects granted ethical approval by another Reviewing HREC and granted Research Governance Authorisation by the Eye and Ear

All research Adverse Events occurring at the Eye and Ear or involving an Eye and Ear patient must be reported:

1. to the Eye and Ear Research Office
 2. as soon as possible and within 72 hours of occurrence
 3. using the EAE Single Adverse Event Report Form
 4. to the Reviewing HREC as required by the Reviewing HREC:
 - a. If submitted to the Reviewing HREC then submit Reviewing HREC response to the Eye and Ear Research Office
2. Clinical Trials

Roles and responsibilities

Responsibilities, procedures and flowcharts for safety monitoring and reporting in clinical trials are outlined in full in the *NHMRC Guidance: Safety monitoring and reporting in clinical trials involving therapeutic goods* (NHMRC; November 2016)

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and briefly in the table below. Definitions of terms used in the table are detailed in the 'Definitions' section.

Flowcharts of safety reporting processes, reproduced from the NHMRC document *Safety monitoring and reporting in clinical trials involving therapeutic goods* (November 2016), are detailed in Appendix 1 and 2:

- Appendix 1 – Safety Reporting Processes Flowchart for **drug** trials (Investigational Medicinal Product (IMP) trials)
- Appendix 2 – Safety Reporting Processes Flowchart for **device** trials (Investigational Medical Device (IMD) trials)

In brief:

- the Sponsor has primary responsibility for monitoring the ongoing safety of the clinical trial;
- The investigator should provide the Sponsor with all relevant information for the Sponsor to conduct a safety analysis;
- The HREC has responsibility to ensure the Sponsor's arrangements are sufficiently independent and commensurate with the risk, size and complexity of the trial;
- The Institution should assess whether any safety reports are a risk.

Procedures

1. Pre-Approval

The Sponsor is responsible for ensuring that the Clinical Trial Protocol has clear sections describing the:

- a. process for the assessment and management of risk; and
- b. safety reporting definitions, procedures, responsibilities and reporting timelines (refer to the Data Safety Monitoring Board (DSMB) section below); and
- c. reporting of any serious adverse events that do not require immediate reporting

The Reviewing HREC may request amendments to the Project Proposal / Protocol to ensure the safety monitoring and reporting requirements are adequate for the research project.

2. Annual Safety Report

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The Annual Safety Report should include the details outlined in the Guidelines NHMRC Guidance: Safety monitoring and reporting in clinical trials involving therapeutic goods (NHMRC; November 2016)

The Annual Safety Report is due

- a. to the Reviewing HREC when the Sponsor has prepared the Report; or
- b. is due at the same time as the project's Annual Progress Report unless by prior agreement of alternate timing.

The Annual Safety Report may be submitted using the Annual Safety Report Form [DHHS supplied].

The Reviewing HREC and Research Office has the discretion to request more frequent reporting for specific trials, such as early phase trials. Such a request may be stated on the initial ethics approval letter / Research Governance Authorisation letter or during the conduct of the trial.

3. Procedure for research projects granted ethical approval by the Eye and Ear HREC.

Sponsors (via the PI) must provide the Reviewing HREC with an Annual Safety Report including a clear summary of the evolving safety profile for a trial.

4. Procedure for research projects granted ethical approval by another Reviewing HREC and granted Research Governance Authorisation by the Eye and Ear.

Sponsors (via the Eye and Ear site PI) must provide the Research Office with an Annual Safety Report including a clear summary of the evolving safety profile for a trial.

5. Annual update of the Investigators Brochure

Sponsors must provide the Reviewing HREC with an annual update of the Investigator's Brochure or, where applicable, Product Information sheet.

Sponsors must provide the Reviewing HREC with any Addenda to the Investigator's Brochure or, where applicable, Product information sheet.

6. Reports from Data Safety Monitoring Boards (DSMB)

Principal Investigators (PI) must forward all Data Safety Monitoring Board (DSMB) Reports to the HREC as they arise.

DSMB Reports must be accompanied by the Eye and Ear HREC DSMB Reporting Form [Eye and Ear supplied] signed by the PI stating that they have reviewed the report and, if required, that they are addressing any issues associated with the content of the report.

Any DSMB reports are included in the agenda papers at the next scheduled Eye and Ear HREC meeting. The HREC reviews the report and any queries, comments or clarifications raised are sent to the PI by the HREC Secretary within 10 working days of the meeting. If no queries are raised, the report is accepted, filed in the Research Office project file and the PI is notified.

7. Adverse Events

PI to report all Adverse Events to the Sponsor according to the Protocol.

8. Serious Adverse Events (SAEs) and Serious Adverse Reactions (SARs)

PIs must report all SAEs (unless not required in the Protocol) to the Sponsor within 24 hours of becoming aware of the SAE.

9. All Serious Adverse Events or Reactions that occur as part of a Clinical Trial occurring at the Eye and Ear or involving an Eye and Ear patient must be reported to:
 - a. to EAE Research Office
 - b. as soon as possible and within 72 hours of the PI becoming aware of the SAE
 - c. using the EAE Single Adverse Event Report Form
10. Additional procedure for research projects granted ethical approval by another Reviewing HREC and granted Research Governance Authorisation by the Eye and Ear

All research Serious Adverse Events or Reactions occurring at the Eye and Ear or involving an Eye and Ear patient must be reported:

- a. to EAE Research Office
- b. as soon as possible and within 72 hours of the PI becoming aware of the SAE
- c. using the EAE Single Adverse Event Report Form
- d. to the Reviewing HREC as required by the Reviewing HREC
 - If submitted to the Reviewing HREC then submit Reviewing HREC response to the Eye and Ear Research Office

11. All Significant Safety Issues

All Significant Safety Issues occurring at the RVEEH site, including Urgent Safety Measures, should be notified:

- a. By the PI to the Sponsor as soon as possible and within 72 hours of occurrence
- b. By the PI to the Institution as soon as possible and within 72 hours of occurrence
- c. By the sponsor (via the PI) to the Research Office at the RVEEH, and
- d. as soon as possible and within 15 days of occurrence using the Safety Report Form [supplied by DHHS] reported to the Reviewing HREC; and if the Eye and Ear HREC is not the Reviewing HREC, to the Eye and Ear Research Office

12. Amendments arising from Adverse Events

- a. Amendments should be submitted to the RGO and HREC without undue delay
- b. The PI of the site should submit the request for amendment to the Reviewing HREC.
- c. The amendment should be submitted without undue delay and no later than 15 days of the sponsor being aware of the issue
- d. The amendment should be submitted as per the Reviewing HREC requirements

13. Temporary halt to the study should be notified without undue delay and within 15 days

- a. The PI of the site should submit the notification to the Reviewing HREC
- b. The report should be submitted within 15 days
- c. The report should be submitted on the Safety Report [supplied by DHHS]

14. Early termination of a trial site for safety reasons should be notified without undue delay and within 72 hours

- a. The PI of the site should submit the notification to the Reviewing HREC and to the Eye and Ear Research Governance Officer and the HREC
- b. The report should be submitted within 15 days
- c. The report should be submitted on the Safety Report [supplied by DHHS]

Section D: Review Procedure

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1. All Reports are reviewed by the HREC Chair for seriousness, expectedness and relatedness.
2. Research Project Deviations and Non-Serious Breaches and Suspected Breaches will be reviewed by the HREC Chair and only referred to the HREC if required
3. Research Project Violations or Serious Breaches will be reviewed by the HREC Chair and then referred to the HREC
4. SAEs may be referred to the HREC for review
5. SAEs may be referred to other relevant health professionals on the HREC or clinical trial pharmacist
6. The HREC or HREC Chair is then required to determine the appropriate course of action. This may include:
 1. no action, information on file of the occurrence;
 2. request for additional information or clarification from the investigator;
 3. request for an amendment to the Protocol and/or Participant Information & Consent Form;
 4. suspension of ethical approval and project halted (refer to RS1.5 HREC Procedure for Suspension or Withdrawal of Approval for Conduct of Research Projects);
 5. suspension of the authorisation to conduct the study at the Eye and Ear and increased monitoring of the project; and
 6. Where the event is confirmed through the Chair's review as **serious**, **expected and related** to the study procedure or investigational medicine, device or biological, the HREC Chair must notify the Executive Director Medical Services (EDMS)/Chief Medical Officer (CMO), or delegate.
 1. If needed, the EDMS/CMO, via the Research Office will, instruct the Principal Investigators to log the event in Riskman.
 2. Upon entry, the details of the event are reviewed by the EDMS/CMO who decides if the Victorian Managed Insurance Authority (VMIA) is to be notified.

Outcome:

To ensure that all research projects are monitored to ensure research participant / patient safety, health and well-being.

To ensure that if an adverse event does occur, it is properly documented, reported on and monitored until such time as the incident report can be closed.

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Definitions:

For all research projects

Institution	The organisation where the research is being conducted.
Monitoring	Monitoring of research refers to the process of verifying that the conduct of research conforms to the approved proposal.
Research Project Deviation	A Research Project Deviation is a less serious breach, divergence or departure from the requirements of Good Clinical Practice or the Research Proposal/Protocol and does not have a significant impact on the continued safety or rights of participants or the reliability and robustness of the data.
Research Project Violation	<p>A Research Project Violation is a serious breach of Good Clinical Practice or the Research Proposal/Protocol that is likely to affect to a significant degree</p> <p>the safety or rights of a research participant, or</p> <p>the reliability and robustness of the data generated in the research project</p> <p>A Research Project Violation may, in some cases result in the exclusion of a participant from the study, exclusion of a participant's data from the results of a study or in some cases a charge of research misconduct.</p>

For all Clinical Trials

Annual Safety Report	<p>Summary of all new available safety information relevant to a trial that is received over a 12 month period.</p> <p>Note: the Executive Summary of safety information produced for international regulators, such as a Development Safety Update report (DSUR) may serve as the Annual Safety Report (a full DSUR is not required).</p>
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<p>Clinical Trial</p>	<p>1. A 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.</p> <p>Clinical trial interventions include but are not restricted to:</p> <ul style="list-style-type: none"> • experimental drugs • cells and other biological products • vaccines • medical devices • surgical and other medical treatments and procedures • psychotherapeutic and behavioural therapies • health service changes • preventive care strategies and • educational interventions. <p>Researchers may also conduct clinical trials to evaluate diagnostic or screening tests and new ways to detect and treat disease.</p> <p>WHO definition</p> <p>and/or</p> <p>2. Any investigation in human subjects intended to discover or verify the clinical, pharmacological and/or other pharmacodynamic effects of an investigational product(s), and/or to identify any adverse reactions to an investigational product(s), and/or to study absorption, distribution, metabolism, and excretion of an investigational product(s) with the object of ascertaining its safety and/or efficacy. The terms clinical trial and clinical study are synonymous.</p>
<p>Data Safety Monitoring Board</p>	<p>An independent and multi-disciplinary 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.</p>

<p>Non-serious Breach (previously Protocol Deviation)</p>	<p>A Non-Serious Breach/Deviation is any breach, divergence or departure from the requirements of Good Clinical Practice or the clinical trial protocol and does not have a significant impact on the continued safety or rights of participants or the reliability and robustness of the data generated in the clinical trial.</p> <p><i>Also refer to definition for Serious Breach.</i></p> <p><i>Also refer to definition for Suspected Breach.</i></p>
<p>Serious Breach (previously Protocol Violation)</p>	<p>A Serious Breach is a breach of Good Clinical Practice or the protocol that is likely to affect to a significant degree:</p> <ul style="list-style-type: none"> a. the safety or rights of a research participant, or b. the reliability and robustness of the data generated in the research project. <p><i>Also refer to definition of Non-Serious Breach.</i></p>
<p>Significant Safety Issue (SSI)</p>	<p>A safety issue that could adversely affect the safety of participants or materially impact on the continued ethical acceptability or conduct of the trial.</p>
<p>Sponsor</p>	<p>The Sponsor of a clinical trial is defined as 'an individual, organisation or group taking on responsibility for securing the arrangements to initiate, manage and finance a study'. <i>GCP Guidelines</i></p> <p>Many sponsor functions may be delegated to third parties, such as clinical research organisations/centres, Data Safety Monitoring Boards or Coordinating Principal Investigators, provided that arrangements are in place for oversight of any delegated activities.</p>
<p>Suspected Breach</p>	<p>A Suspected Breach is 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.</p>
<p>Urgent Safety Measure (USM)</p>	<p>A measure required to be taken in order to eliminate an immediate hazard to a participant's health or safety.</p> <p><i>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.</i></p>

For research which includes use of Investigational Medical Products (IMPs) only

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.
Adverse Reaction (AR)	<p>Any untoward and unintended response to an investigational medicinal product related to any dose administered.</p> <p><i>Comment: All adverse events judged by either the reporting investigator or the sponsor as having a reasonable possibility of a causal relationship to an investigational medicinal product would qualify as adverse reactions. The expression 'reasonable causal relationship' means to convey, in general, that there is evidence or argument to suggest a causal relationship.</i></p> <p><i>Note: The following are examples of types of evidence that would suggest a causal relationship between the investigational product and the adverse event:</i></p> <p><i>A single occurrence of an event that is uncommon and known to be strongly associated with drug exposure (e.g., angioedema, hepatic injury, Stevens-Johnson Syndrome)</i></p>
Investigational Medicinal Product (IMPs)	<p>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.</p> <p><i>Note: This definition includes biologicals used as investigational medicinal products.</i></p>
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.

	<p>SAEs align to Incident Severity rating (ISR) 1 (severe/death/catastrophic) and ISR 2 (Moderate patient impact).</p> <p><i>Note: Life-threatening in the definition of a serious adverse event or serious adverse reaction refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death if it were more severe.</i></p> <p><i>Note: Medical and scientific judgement should be exercised in deciding whether an adverse event/ reaction should be classified as serious in other situations. Important medical events that are not immediately life-threatening or do not result in death or hospitalisation, but may jeopardise the participant or may require intervention to prevent one of the other outcomes listed in the definition above should also be considered serious.</i></p>
Suspected Unexpected Serious Adverse Reaction (SUSAR)	An adverse reaction that is related and both serious and unexpected.

For research which includes use of Investigational Medical Devices (IMDs) only

Adverse Device Effect (ADE)	<p>Adverse event related to the use of an investigational medical device.</p> <p><i>Note: This definition includes adverse events resulting from insufficient or inadequate Instructions for Use, deployment, implantation, installation, or operation, or any malfunction of the investigational medical device. This definition includes any event resulting from use error or from intentional misuse of the investigational medical device.</i></p>
Adverse Event (AE)	<p>Any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in participants, users or other persons, whether or not related to the investigational medical device.</p> <p><i>Note: This definition includes events related to the investigational medical device or the comparator. This definition includes events related to the procedures involved. For users or other persons, this definition is</i></p>

	<i>restricted to events related to investigational medical devices.</i>
Investigational Medical Devices (IMDs)	<p>Medical device being assessed for safety or performance in a clinical investigation</p> <p><i>Note: This includes medical devices already on the market, that are being evaluated for new intended uses, new populations, new materials or design changes.</i></p>
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)	<p>An adverse event that:</p> <ul style="list-style-type: none"> 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 <ul style="list-style-type: none"> 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 foetal distress, foetal death or a congenital abnormality or birth defect. <p><i>Note: Planned hospitalisation for a pre-existing condition, or a procedure required by the Clinical Investigation Plan, without serious deterioration in health, is not considered a serious adverse event."</i></p>
Unanticipated Serious Adverse Device Effect (USADE)	<p>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</p> <p><i>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.</i></p>

Standard:



NSQHS Standard 1: Clinical Governance

- Victoria Health Incident Clinical incident reporting LM 3.3 and LM 3.6 p3

Legislation:

Current Legislation may be sourced at: <http://www.austlii.edu.au/> or Victorian legislation at: <https://www.legislation.vic.gov.au/>

- *Therapeutic Goods Act*

References:

- *National Statement on Ethical Conduct in Human Research* (NHMRC; 2023 and as amended) www.nhmrc.gov.au/book/national-statement-ethical-conduct-human-research
- *Australian Code for the Responsible Conduct of Research* (NHMRC; 2018)
- *NHMRC Guidance: Safety monitoring and reporting in clinical trials involving therapeutic goods* (NHMRC; November 2016) <https://nhmrc.gov.au/about-us/publications/safety-monitoring-and-reporting-clinical-trials-involving-therapeutic-goods>

and the following additional guidance documents:

- Risk-based management and monitoring of Clinical Trials involving Therapeutic Goods (NHMRC; 2018)
- Reporting of Serious Breaches of Good Clinical Practice (GCP) or the Protocol for Trials Involving Therapeutic Goods (NHMRC; 2018)
- Data Safety Monitoring Boards (DSMBs) (NHMRC; 2018)
- Integrated addendum to ICH E6(R1): Guideline for Good Clinical Practice ICH E6(R2) - annotated with TGA comments. November 2016 <https://www.tga.gov.au/publication/note-guidance-good-clinical-practice>
- Pharmacovigilance responsibilities of medicine sponsors; Australian recommendations and requirements. Australian Government Department of Health. Therapeutic Goods Administration. Version 3.01, August 2023

<https://www.tga.gov.au/sites/default/files/2023-08/pharmacovigilance-responsibilities-medicine-sponsors-2023.pdf>

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- Australian Clinical Trial Handbook (August 2021)
<https://www.tga.gov.au/sites/default/files/australian-clinical-trial-handbook.pdf>
- VMIA Guidelines for Clinical Trials for Victorian Public Hospitals
<https://www.vmia.vic.gov.au/-/media/Internet/Content-Documents/Risk/Guides-and-Publications/clinical-trials/Clinical-Trials-Guide.pdf>
- Department of Health and Human Services Clinical Trials website
<https://www.australianclinicaltrials.gov.au/>

Linked Policy & Procedure:

- Research Policy
- HREC Procedure Suspension or Withdrawal of Approval for Conduct of Research Projects

Approval/Committees:

Eye and Ear Human Research Ethics Committee

Responsible Executive:

Executive Director Medical Services/Chief Medical Officer

Document Author:

Manager Research

Evaluation:

Patient safety.

Compliance with current legislation, regulations, industry standards, guidelines, codes of conduct and codes of ethics.

Procedure Review:

This procedure will be reviewed at least every 3 years.

Author/ Co-Authors:

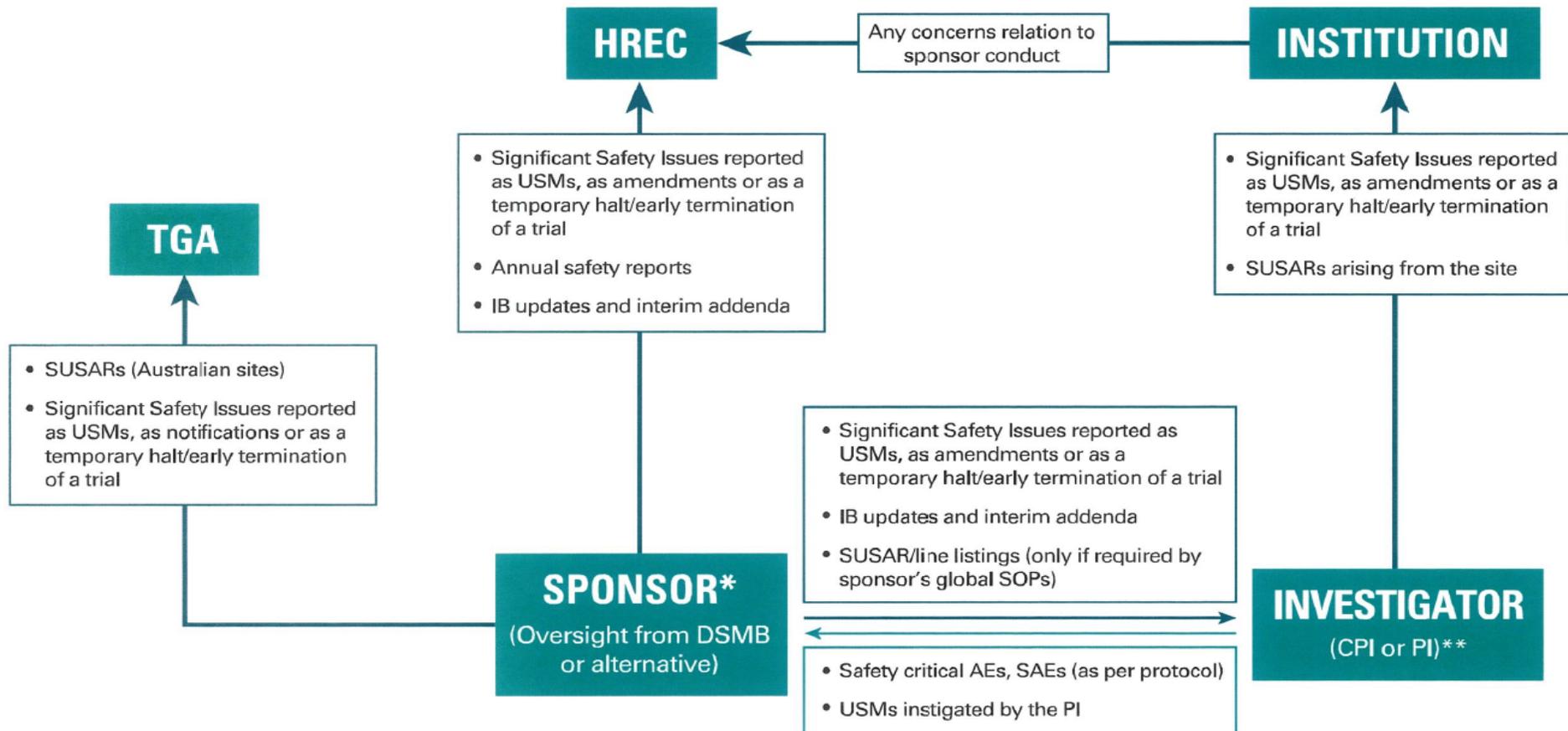
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Name	Position	Service / Directorate
Dr Birinder Giddey	Executive Director Medical Services/Chief Medical Officer	Medical Services
Dr Marc Sarossy	Chair, Human Research Ethics Committee	Medical Services
Assoc Prof Peter Keller	Research Manager	Medical Services
Ms Swetha Raghavan	Administrative Officer	Medical Services

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Details	
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Legislation Section:	E – Patient’s Rights F – Privacy
Review Date(s):	September 2019, 13 May 2024

Appendix 1: Safety Reporting Processes Flowchart – for Drug Trials (Investigational Medicinal Product - IMP)



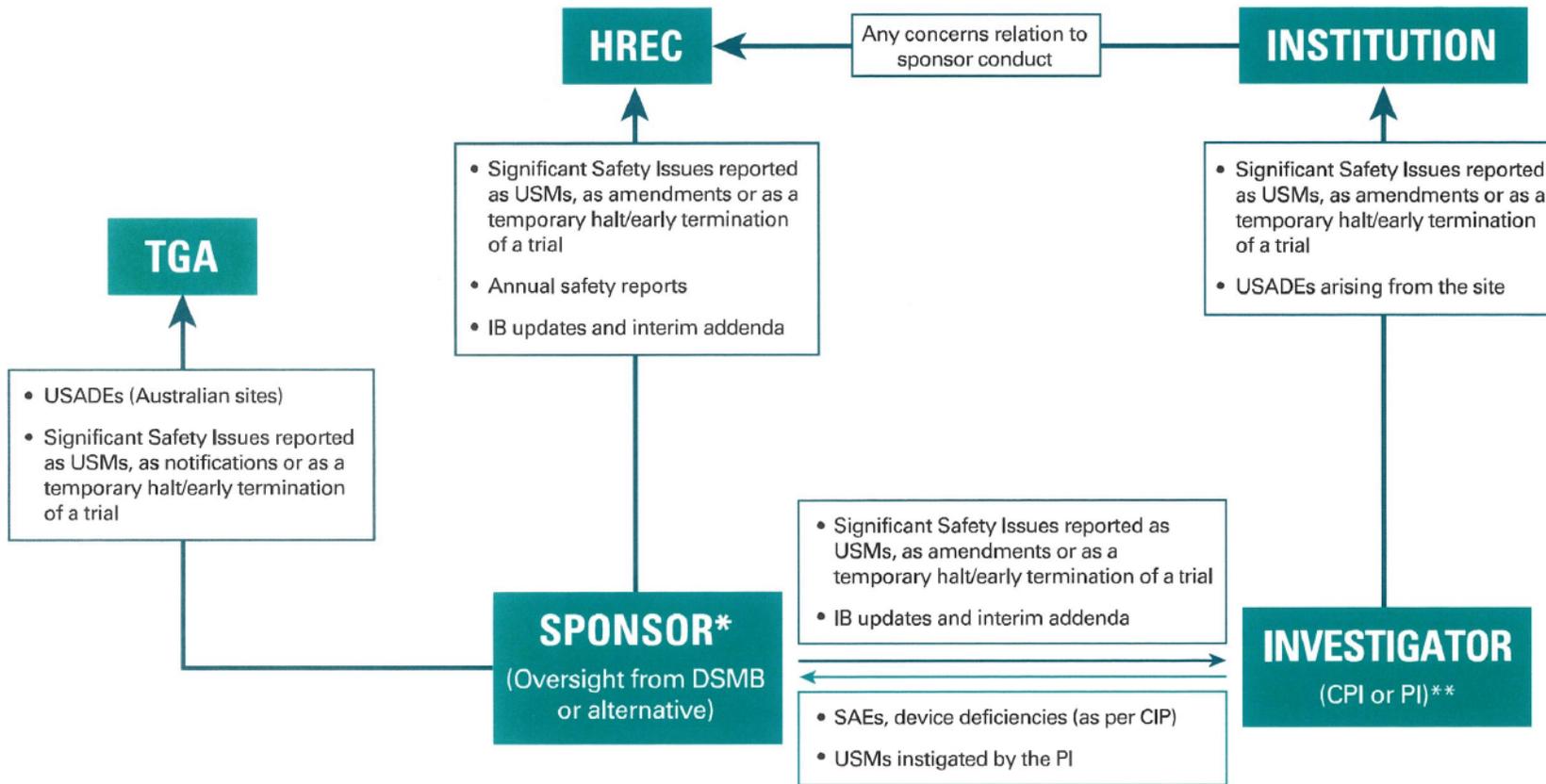
KEY

- AE – Adverse Event
- DSMB – Data Safety Monitoring Board
- SAE – Serious Adverse Event
- SUSAR – Suspected Unexpected Serious Adverse Reaction
- IB – Investigator’s Brochure
- PI – Product Information
- PI – Principal Investigator
- CPI – Co-ordinating Principal Investigator
- SOP – Standard Operating Procedure
- USM – Urgent Safety Measure

* The sponsor (or their delegate) should report to all parties in accordance with the timelines indicated within this document.
 **The CPI should be provided with all correspondence sent by the sponsor to PIs and/or the HREC.

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Appendix 2: Safety Reporting Processes Flowchart – for Device Trials (Investigational Medicinal Product - IMP)



KEY

- AE – Adverse Event
- DSMB – Data Safety Monitoring Board
- SAE – Serious Adverse Event
- USADE – Unanticipated Serious Adverse Device Effect
- USM – Urgent Safety Measure
- CIP – Clinical Investigation Plan
- IB – Investigator’s Brochure
- IFU – Instructions for Use
- PI – Principal Investigator
- CPI – Co-ordinating Principal Investigator
- SOP – Standard Operating Procedure
- HREC – Human Research Ethics Committee

* The sponsor (or their delegate) should report to all parties in accordance with the timelines indicated within this document.
 **The CPI should be provided with all correspondence sent by the sponsor to PIs and/or the HREC.

Appendix 3: Summary chart of roles and responsibilities and procedures for each element of monitoring and safety reporting

Non-Clinical Research (i.e., use of data/surveys of staff)

Details	PI role	Sponsor role	HREC role	Institution role (Research Governance Officer)
Annual Report and Self Audit	Submit Annual Report, including Self Audit Report to EAE RO Use EAE Annual Report Form		Review All Reports added to HREC Agenda	Review
Final Report	Submit Final Report to EAE RO Use EAE Final Report Form		Review All Reports added to HREC Agenda	Review
Research Project Deviation and Research Project Violation	Submit EAE Research Project Deviation and/or Violation Reporting Form to EAE RO		Research Project Deviations reviewed and noted by the HREC Chair. Research Project Violation reviewed by the HREC Chair and added to HREC Agenda	Review

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Clinical Research

Details		PI role	Sponsor role	HREC role	Research Governance Officer role
Annual Report and Self Audit		Submit Annual Report, including Self Audit Report to EAE RO Use EAE Annual Report form		Review All Reports added to HREC mtg Agenda	Review
Final Report		Submit Final Report to EAE RO Use <u>EAE Final Report Form</u>		Review All Reports added to HREC mtg Agenda	Review
Adverse Events (AEs)	Unrelated	PI report all AEs to EAE RO Use <u>EAE Adverse Event Reporting Form</u>		HREC Chair to review If 'unrelated' confirmed then not added to Agenda and acknowledgement sent to PI	Review
	Related	PI report all AEs to EAE RO Use <u>EAE Adverse Event Reporting Form</u>		HREC Chair to review All Related Reports added to HREC Agenda	Review
Research Project Deviation Research Project Violation		Submit <u>EAE Research Project Deviation and/or Violation Reporting Form</u> to EAE RO		Research Project Deviations reviewed and noted by the HREC Chair. Research Project Violation reviewed by the HREC Chair and added to HREC Agenda	Review

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Clinical Trials

Details	PI role	Sponsor role	HREC role	Institution role
Annual Report and Self Audit	Submit Annual Report to EAE RO Use EAE Annual Report form		Review All Reports added to HREC mtg Agenda	Review
Final Report	Submit Final Report to EAE RO Use EAE Final Report Form		Review All Reports added to HREC mtg Agenda	Review
Annual Safety Report	If EAE Sponsor, submit Annual Safety Report to EAE RO Use Annual Safety Report Form [DHHS supplied]	Submit Annual Safety Report to EAE RO	Review All Annual Safety Reports added to HREC meeting agenda	Review
Investigator Brochure updates		Submit annual IB/Product Information updates and / or addenda	HREC Chair to review	Review
Data Safety Monitoring Board Reports	Principal Investigators (PI) must forward all Data Safety Monitoring Board (DSMB) Reports to the HREC as they arise.	Provide DSMB Report to the PI	HREC Chair to review DSMB reports are included in the agenda papers at the next scheduled Eye and Ear HREC meeting	Review

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PROCEDURE		<u>Use EAE DSMB Reporting Form</u>			
Adverse Events (AEs)	Unrelated	<p>PI report all AEs to Sponsor (as per Protocol)</p> <p>PI does not need to report individual unrelated AEs to EAE HREC or RO</p> <p>If EAE is the Sponsor, submit <u>EAE Adverse Event Reporting Form</u> to RO</p>	<p>Sponsor to compile and review all AEs and include as part of annual safety report</p> <p>Sponsor (EAE is not Sponsor) does not need to report individual AEs to EAE HREC or RO</p>		
	Related	<p>PI report all AEs to Sponsor (as per Protocol)</p> <p>PI does not need to report individual related AEs to EAE HREC or RO unless the EAE is the Sponsor.</p> <p>If EAE is the Sponsor, submit <u>EAE Adverse Event Reporting Form</u> to RO</p>	<p>Sponsor to compile and review all AEs and include as part of annual safety report</p> <p>Sponsor (not EAE) does not need to report individual AEs to EAE HREC or RO</p>		
Serious Adverse Events (SAEs)/Serious Adverse Reactions(SARs) including SUSARs / USADEs that do	Related and unrelated	<p>PI report all SAEs to Sponsor (as per Protocol) and within 24 hours</p> <p>PI to report individual SAEs involving EAE sites and/or</p>	<p>Sponsor to compile and review all SAEs and include as part of Annual Safety Report.</p> <p>Sponsor (EAE is not Sponsor) does not need</p>		

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<p>not meet the criteria of Serious Safety Issue (SSI) or Urgent Safety Measure (USM)</p>		<p>patients using <u>EAE Adverse Event Reporting Form</u> to RO</p> <p>If EAE is the Sponsor, submit <u>EAE Adverse Event Reporting Form</u> to RO</p>	<p>to report individual SAEs involving EAE sites and/or patients if it is an SAE that does not meet the criteria of SSI or USM</p>		
<p>Significant Safety Issue (SSI)</p>	<p>Meet definition of Urgent Safety Measure</p>	<p>Notify the Sponsor of Urgent Safety Measure as soon as possible and within 24 hours of becoming aware of the event.</p> <p>Inform Reviewing HREC EAE is not Sponsor Inform investigational sites within 72 hours</p> <p>Submit Amendment without undue delay</p> <p>Notify if a temporary halt for safety reason</p> <p>Notify if early termination of a trial for safety reason</p>	<p>Inform</p> <ul style="list-style-type: none"> • Investigators • Reviewing HREC • Research Office • TGA <p>within 72 hours</p> <p>Submit Amendment without undue delay and within 15 days</p> <p>Notify if a temporary halt for safety reason without undue delay and within 15 days</p> <p>Notify if early termination of a trial for safety reason without undue delay and within 15 days</p>	<p>HREC Chair to review</p> <p>Decision ratified at next HREC meeting</p>	<p>Review</p>

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	All other SSIs	<p>Inform Reviewing HREC within 72 hours</p> <p>Inform investigational sites within 72 hours</p>	<p>Reported to</p> <ul style="list-style-type: none"> Investigators Reviewing HREC RO TGA <p>within 15 days</p> <p>Submit Amendment without undue delay and within 15 days</p> <p>Notify if a temporary halt for safety reason without undue delay and within 15 days</p> <p>Notify if early termination of a trial for safety reason without undue delay and within 15 days</p>	<p>HREC Chair to review</p> <p>Decision ratified at next HREC meeting</p>	Review
SUSARs USADEs	Fatal / life threatening				
	Involving EAE site and/or EAE patient	<p>PI to report SUSAR/USADE to RO within 72 hours</p> <p>Report to Sponsor within 72 hours</p>	<p>Sponsor reports fatal / life threatening SUSARs at all Australian sites to</p> <ul style="list-style-type: none"> HREC RO TGA <p>Immediately and within 7 days</p>	<p>HREC Chair to review</p> <p>Decision ratified at next HREC meeting</p>	Review

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			SSI reported as USMs		
			SUSAR 6 monthly line listings are no longer required		
	Not associated with EAE				
All other SUSARs					
	Involving EAE site and/or EAE patient	Report to RO within 72 hours	<p>Sponsor reports SUSARs at all Australian sites to</p> <ul style="list-style-type: none"> • HREC • RO • TGA <p>immediately and within 15 days</p> <p>SSI reported as USMs</p> <p>SUSAR 6 monthly line listings are no longer required</p>	<p>HREC Chair to review</p> <p>Decision ratified at next HREC meeting</p>	Review
	Not associated with EAE				
Breaches of GCP and/or the Protocol	Non-serious Breach	PI should report Non-Serious Breaches to the Sponsor within 7 days using the Sponsor supplied Form or <u>Non-serious Breach Form</u> [DHHS supplied]	Non-Serious Breaches should be reported to the Research Office	<p>HREC Chair to review</p> <p>Decision ratified at next HREC meeting</p>	

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		If EAE is the Sponsor: PI must report Non-Serious Breaches to the RO within 72 hours using the <u>Non-serious Breach Form</u> [DHHS supplied] as instructed on the Research Office website.			
	Serious Breach	<p>PI should report all Serious Breaches within 72 hours using the <u>Serious Breach Report Form (Sponsor)</u> [DHHS supplied] as instructed on the Research Office website.</p> <p>If EAE is the Sponsor: PI must report Serious Breaches to the RO within 72 hours using the <u>Serious Breach Report Form</u> [DHHS supplied] as instructed on the Research Office website.</p>	<p>The Sponsor must report Serious Breaches to the Reviewing HREC within 7 days.</p> <p>The Sponsor must report Serious Breaches involving the Eye and Ear Hospital, to the Research Office within 72 hours.</p> <p>Submit the <u>Serious Breach Report Form (Sponsor)</u> [DHHS supplied] as instructed on the Research Office website.</p>	<p>HREC Chair to review</p> <p>Decision ratified at next HREC meeting</p>	Review
	Suspected Breach	A third party (e.g. individual / institution) can report a suspected breach of Good Clinical Practice or the protocol directly to the reviewing HREC		<p>HREC Chair to review</p> <p>Decision ratified at next HREC meeting</p>	Review

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		<p>without reporting through the Sponsor.</p> <p>Submit the <u>Suspected Breach Report Form (Third Party)</u> [DHHS supplied] as instructed on the Research Office website.</p>			
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HREC

Advise the TGA, investigators and their institutions of any decision to withdraw approval.

NOTE: this includes advising the Institution, via the Executive Director Medical Services/Chief Medical Officer of any Urgent Safety Measures advised within 24 hours of becoming aware of the event.

The HREC will review safety reporting information received from the sponsor and satisfy itself that safety monitoring is appropriate, ongoing and that proportionate systems are in place to mitigate and manage risk.