Ethics and Research Governance Workshop Series

Safety Submissions

Dr Cameron Lutman

Research Ethics and Governance Coordinator

NSW GOVERNMENT Health
South Western Sydney Local Health District

Ethics and Research Governance Workshop Series

- **Workshop 4**: Research Contracts and Agreements – 22 May 2023, 2:30-3:30pm
  - *Please register for this workshop on our website.*

- **Statistics Workshop -** 17 October 2023, 2:30-3:30pm
  - *Further information and the registration link is available on our website*

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Today's Topic

Safety Submissions:

- Safety definitions
- The different kinds of safety submissions
- Reporting requirements
- Safety reporting for non-clinical trial studies
- How to submit

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Safety Reporting

- It is important to collect data when conducting clinical trials on the effects of the study intervention on participants, in order ***to ensure participant safety***.

- Thorough record keeping, and the ***prompt and appropriate reporting*** of safety matters is critical to protecting participants, including both those enrolled in a trial, and those receiving the treatment after it has become the standard of care.

Clinical Trial Types

Therapeutic Goods Trials

Trials investigating the safety and/or effectiveness of ***medicines, biologicals or medical devices.***

Non-Therapeutic Goods Trials

Trials other than a Therapeutic Goods Trial ***(e.g. radiotherapy, surgery, psychotherapy trials).***

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Definitions

Guiding document

NHMRC guidance on Safety Monitoring and Reporting in Clinical Trials Involving Therapeutic Goods

- https://www.nhmrc.gov.au/about-us/publications/safety-monitoring-and-reporting-clinical-trials-involving-therapeutic-goods

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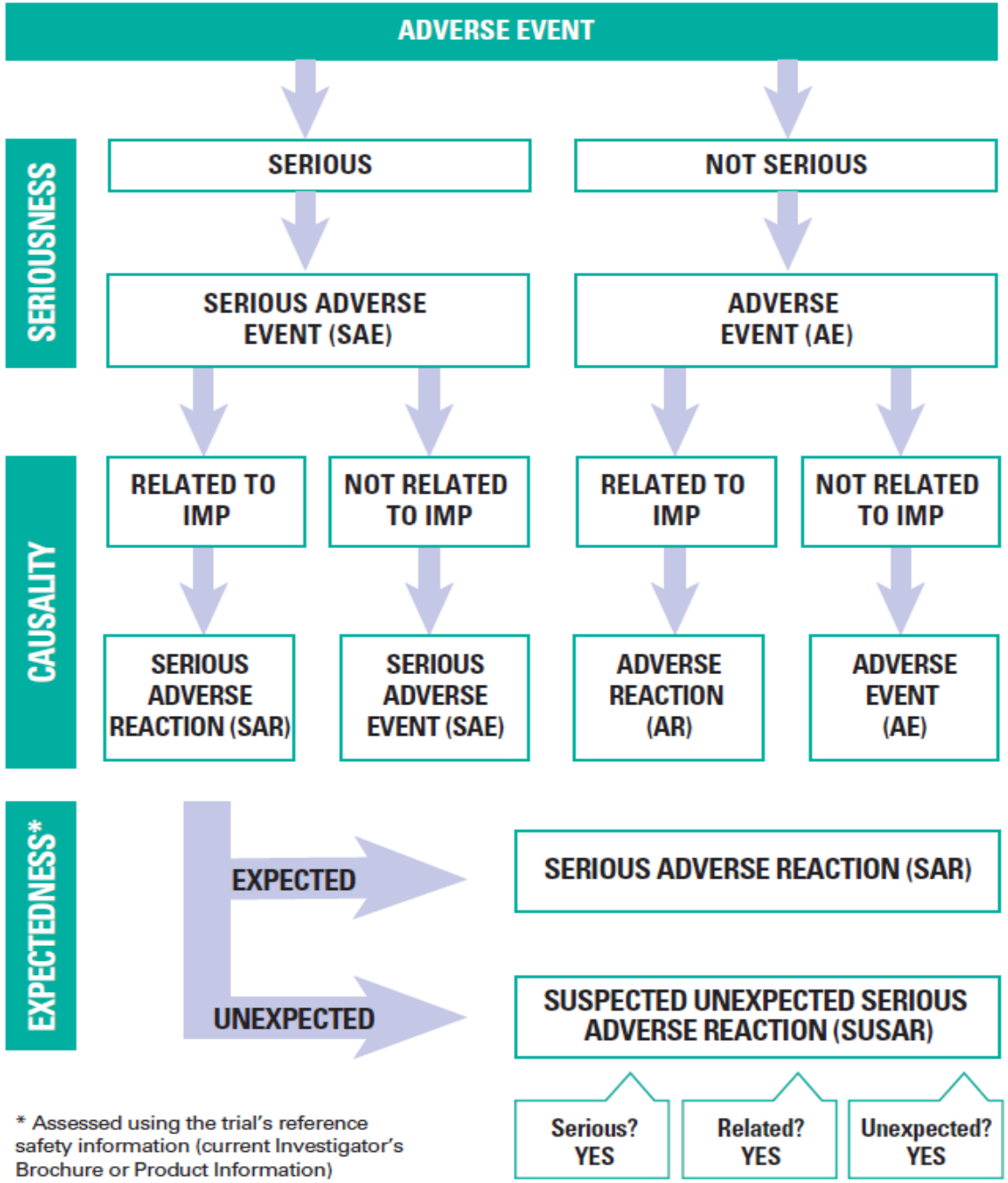
B. Safety Reporting Assessment Flowchart: IMP Trial



* Assessed using the trial's reference safety information (current Investigator's Brochure or Product Information)

IMP: Investigational Medicinal Product (IMP)

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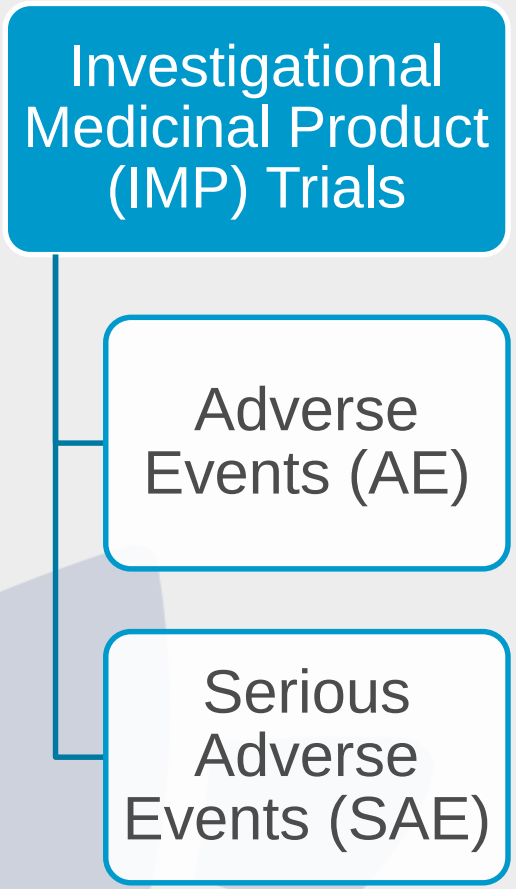
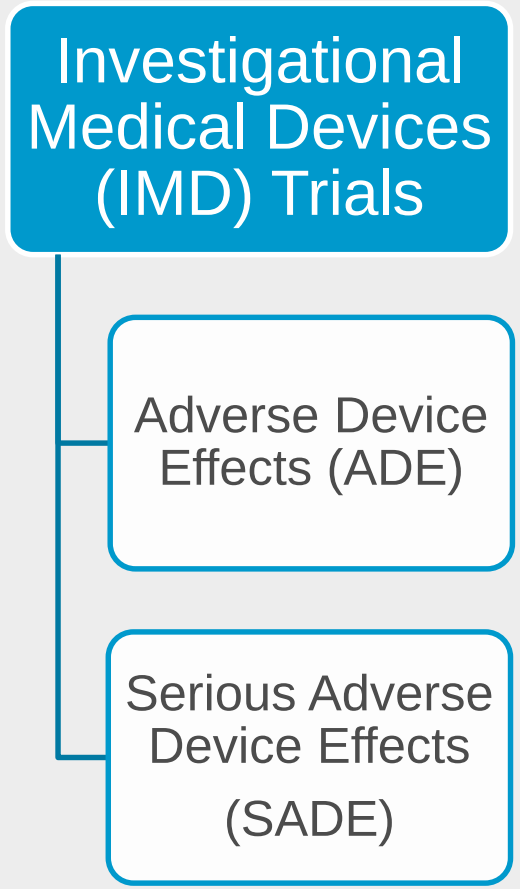
IMP vs. IMD





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Adverse Events (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.”

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Serious Adverse Events (SAE)

Serious Adverse Events (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."

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Serious Adverse Events (SAE)

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.

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.

Serious Adverse Events (SAE)

- It is also important to check the way that “Serious” is defined in the study Protocol.
- Researchers should always ***read the study Protocol carefully***, as Sponsors may include other events in the ***definition of Serious***, depending on the nature of the study.

Adverse Device Effect (ADE)

- **Adverse Device Effect (ADE):** “Adverse event related to the use of an investigational medical device.”
  - “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.”

Serious Adverse Device Effect (SADE)

Serious Adverse Device Effect (SADE): An adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event.

Further Safety Submission Types

- SUSAR
- USADE
- URSAE
- USM
- SSI

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Suspected Unexpected Serious Adverse Reaction (SUSAR)

Suspected Unexpected Serious Adverse Reaction (SUSAR): An adverse reaction that is both serious and unexpected.

Unanticipated Serious Adverse Device Effects (USADEs)

Unanticipated Serious Adverse Device Effects (USADEs): A 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 (and/or Investigator's Brochure/Instructions for Use).

Unexpected & Related SAEs (URSAE):

Unexpected & Related SAEs (URSAE): The terms ‘adverse reaction’ and ‘suspected unexpected serious adverse reaction’ (SUSAR) are not appropriate for device trials (as no reaction is taking place), so they are also not appropriate for non-therapeutic goods trials.

Unexpected & Related SAEs (URSAE):

The SUSAR-equivalent for a non-therapeutic good trial would be an Unexpected and Related Serious Adverse Event (URSAE). An adverse event that is:

- **Serious –** meets the definition of a serious adverse event
- **Related –** resulted from administration of the trial intervention
- **Unexpected –** the event is not described in the protocol as an expected occurrence.

Submitting SUSARs, USADEs, and URSAEs

- If the SUSAR, USADE, or URSAE occurred at an SWSLHD site, they should be submitted to SWSLHD Research Governance using the Local SUSAR/USADE/URSAE Notification Form via email to SWSLHD-Ethics@health.nsw.gov.au These must be reported by the Principal Investigator to SWSLHD Research Governance within 72 hours of being aware of the event.

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Urgent Safety Measure (USM):

Urgent Safety Measure (USM): A measure required to be taken in order to eliminate an immediate hazard to a participant's health or safety.

This is typically reportable as part of a Significant Safety Issue (SSI), which will be covered in the next slide.

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Significant Safety Issue (SSI):

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. NOTE: Some SSIs are also reportable as a USM.

If SWSLHD is the lead HREC, this should be submitted to SWSLHD Ethics using the Significant Safety Issue Notification Form *via* email to SWSLHD-Ethics@health.nsw.gov.au

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Significant Safety Issue (SSI):

If the SSI is also reportable as a USM, the **sponsor is responsible for reporting to the lead HREC within 72 hours** of being made aware of the event. If the SSI is not also a USM, then the sponsor is responsible for reporting to the lead HREC within 15 days of being made aware of the event.

NOTE: For any type of SSI, the Principal Investigator also has the responsibility:

- for **reporting to the Sponsor within 24 hours**.
- for **reporting to SWSLHD Research Governance within 72 hours**

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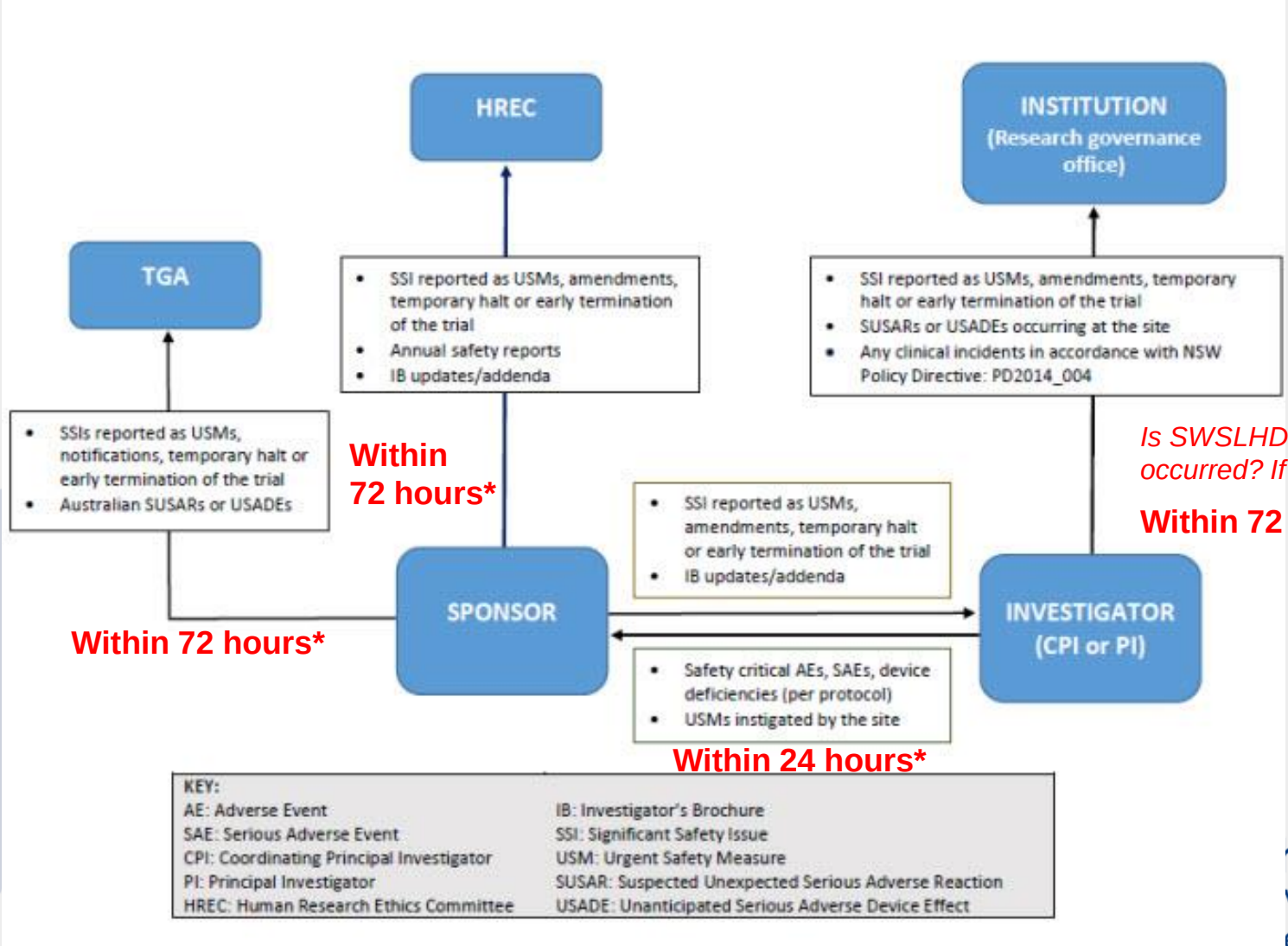
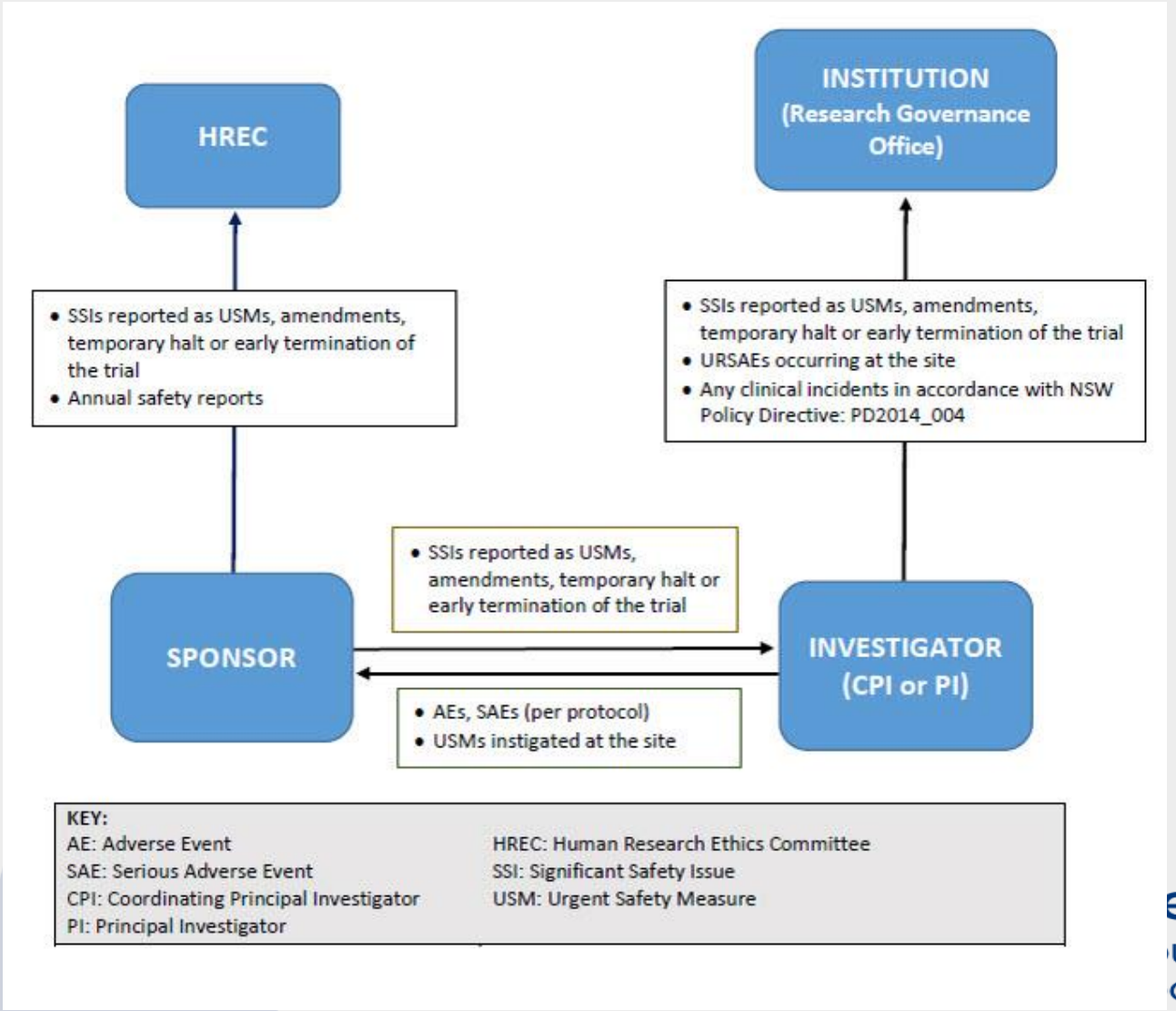
NHMRC Reporting Requirements – Therapeutic Goods Trials



NHMRC Reporting Requirements – Non-Therapeutic Goods Trials



View safety notification summary table

Results

(6 results)

Type of event	Who reports	To whom	When	How
Significant Safety Issue (SSI) implemented as an Urgent Safety Measure (USM)	Sponsor/Delegate	The reviewing HREC (and all investigators participating in the study)	As soon as possible and no later than 72 hours of the sponsor becoming aware of the USM	SSI Notification Form; Sponsor's template
Significant Safety Issue (SSI) not implemented as an Urgent Safety Measure (USM)	Sponsor/Delegate	The reviewing HREC (and all investigators participating in the study)	Within 15 days of the sponsor becoming aware of the SSI	SSI Notification Form; Sponsor's template
All Significant Safety Issues (SSIs)	Principal Investigator	The RGO for the site where the event occurred	As soon as possible and no later than 72 hours of the PI becoming aware of the SSI	SSI Notification Form; Sponsor's template
Suspected Unexpected Serious Adverse Events (SUSARs) and Unanticipated Serious Adverse Device Effects (USADEs) occurring at the site	Principal Investigator	The RGO for the site where the event occurred	Within 72 hours of the PI becoming aware of the event	SUSAR/USADE/URSAE Notification Form
Investigator's Brochure Updates/Addenda	Sponsor/Delegate	The reviewing HREC	As and when updates are generated	Submitted with a cover sheet or as part of an annual progress/annual safety report
Annual Safety Report	Coordinating Principal Investigator or Sponsor/Delegate	The reviewing HREC	Within annual progress report sent to the HREC or aligned with the safety reporting cycles of global companies	Annual Progress Report or sponsor's template

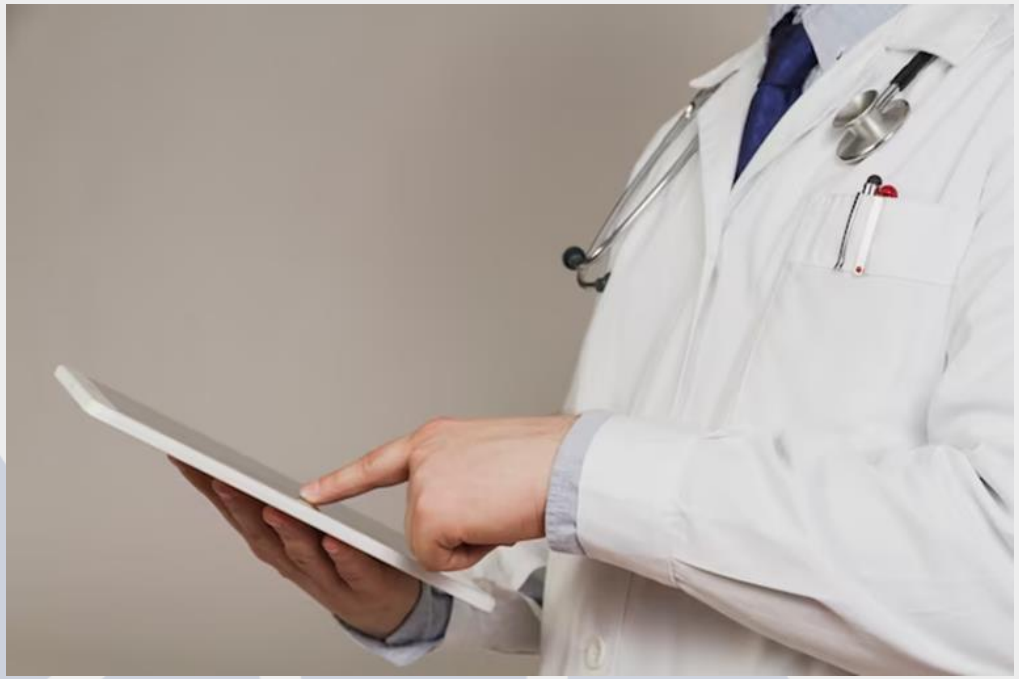
View safety notification summary table

Results

(5 results

Type of event	Who reports	To whom	When	How
Significant Safety Issue (SSI) implemented as an Urgent Safety Measure (USM)	Sponsor/Delegate	The reviewing HREC (and all investigators participating in the study)	As soon as possible and no later than 72 hours of the sponsor becoming aware of the USM	SSI Notification Form; Sponsor's template
Significant Safety Issue (SSI) not implemented as an Urgent Safety Measure (USM)	Sponsor/Delegate	The reviewing HREC (and all investigators participating in the study)	Within 15 days of the sponsor becoming aware of the SSI	SSI Notification Form; Sponsor's template
All Significant Safety Issues (SSIs)	Principal Investigator	The RGO for the site where the event occurred	As soon as possible and no later than 72 hours of the PI becoming aware of the SSI	SSI Notification Form; Sponsor's template
Unexpected & Related Serious Adverse Event (URSAEs) occurring at the site	Principal Investigator	The RGO for the site where the event occurred	Within 72 hours of the PI becoming aware of the event	SUSAR/USADE/URSAE Notification Form
Annual Safety Report	Coordinating Principal Investigator or Sponsor/Delegate	The reviewing HREC	Annually (within the annual progress report)	Annual Progress Report

Protocol Deviations and Serious Breaches



All studies need to be conducted ***in accordance with the ethically approved Protocol***. Any deviation from or non-compliance with the Protocol needs to be recorded, reviewed and reported by the Principal Investigator and Study Sponsor.

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Protocol Deviations and Serious Breaches

Non-compliances are categorised as follows:

DEVIATIONS Any breach, divergence or departure from the requirements of Good Clinical Practice or the study protocol.

Note: To avoid confusion over terminology, the term ‘deviation’ is used by the NHMRC to describe any breach, divergence or departure from the requirements of Good Clinical Practice or the clinical trial protocol, whether minor or major. Although the term ‘violation’ is also widely used in place of ‘deviation’ or to represent a subset of deviations, it is not recommended by NHMRC.

SERIOUS BREACH A divergence from the protocol that has a significant impact on:

- the safety or physical or mental integrity of the subjects of the trial; or
- the scientific value of the trial.

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Protocol Deviations and Serious Breaches

Procedure for Non-Compliance cases:

- Identification
- Documentation
- Reporting

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Protocol Deviations and Serious Breaches

Corrective action/preventive action (CAPA)

- All instances of non-compliance must be reviewed to determine the root cause
- This is addressed via the completion of a Corrective action/preventive action (CAPA form), which is available on our website: https://www.swslhd.health.nsw.gov.au/ethics/forms.html
- The CAPA should be completed and submitted as part of the non-compliance report that is submitted via email to SWSLHD.

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Safety for Non-Clinical Trial Studies

- While non-clinical trial studies have lower levels of risk than clinical trials, safety is still an important concern. The study still needs to be conducted in accordance with the approved Protocol.
- Any Protocol deviations or other safety issues, such as data breaches, confidentiality breaches, or anything else that affects the safety of participants, or the integrity of the study, needs to be reported to the HREC via our email as soon as possible. This should be done in accordance with the non-compliance procedure that we just discussed.

Safety Annual Reporting

- The NHMRC advises that HREC's should be provided with an **annual safety report.**
- This report should include a "clear summary of the evolving safety profile of the trial. This report should allow the HRECs to assess whether ongoing safety monitoring is being conducted appropriately and that the trial's safety monitoring plans are being followed and where necessary, are being adapted to take into account new findings as the trial progresses".

Safety Annual Reporting

The annual safety report should generally include:

- a brief description and analysis of new and relevant findings
- for IMPs not on the Australian Register of Therapeutic Goods, a brief analysis of the safety profile of the IMP and its implications for participants taking into account all available safety data and the results of relevant clinical or non-clinical studies
- a brief discussion of the implications of the safety data to the trial's risk-benefit ratio
- a description of any measures taken or proposed to minimise risks

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Safety Annual Reporting

To submit Annual Safety Reports, this should be done in REGIS by submitting the Annual Report milestone. Investigator Brochure updates should be submitted in REGIS via a General Ethics Amendment.

If SWSLHD is not the lead HREC, it should be submitted to the relevant lead HREC, and that approval and its related documents should be submitted to SWSLHD Research Governance as a Site Amendment (REGIS) / MC Amendment (email).

Safety Annual Reporting: Development Safety Update Reports

- Study sponsors will sometimes prepare a Development Safety Update Report (DSUR) in relation to clinical trials. DSURs are not a requirement in the Australian context, but are required by some international regulators.
- The National Health and Medical Research Council's advice on DSURs is that they can be submitted as part of the Annual Safety Reports that are submitted to HRECs. Alternatively, the Executive Summary of a DSUR can also be included as part of the Annual Safety Report.

How to Submit

- SUSARs, USADEs, SSIs, URSAEs, and Protocol Deviations that need to be submitted to SWSLHD should all be submitted via email, using the appropriate forms. Copies of these forms are available on the OHMR Website and on the SWSLHD website.
- Completed forms should then be submitted our office via SWSLHD-Ethics@health.nsw.gov.au.

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Who to Contact

- SWSLHD:
  - Email: SWSLHD-Ethics@health.nsw.gov.au
  - Phone: 8738 8304
  - Clinical Trials Support Unit email: SWSLHD-ClinicalTrialsSupportUnit@health.nsw.gov.au
- NSW Health Medical Research office email: researchethics@doh.health.nsw.gov.au.

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Helpful Links

- SWSLHD Website: https://www.swslhd.health.nsw.gov.au/ethics/default.html
- OHMR website: https://www.medicalresearch.nsw.gov.au/clinical-trial-safety-monitoring/
- TGA Website: https://www.tga.gov.au/
- Australian Clinical Trials page on Safety Monitoring and Reporting: https://www.australianclinicaltrials.gov.au/guidance-safety-monitoring-and-reporting-clinical-trials

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Questions?

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