Western Health

STANDARD OPERATING PROCEDURE

TGA NOTIFICATION AND SAFETY REPORTING

Standard Operating Procedure

Western Heath

SOP reference	009
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Next Review Date	June 2024
Approved by	Mr Bill Karanatsios, Research Program Director
Signature and date	

Amendment History

VERSION	DATE	AMENDMENT DETAILS
2.0	04 Dec 2015	
3.0	June 2019	Updated to align with MACH SOPs, TGA Australian Clinical Trial Handbook (v2.2 October 2018) and NHMRC Guidance on Safety monitoring and reporting in clinical trials involving therapeutic goods (2016)

1. AIM

To describe the procedures related to the notification of the Therapeutic Goods Administration (TGA) and Safety reporting requirements.

2. SCOPE

Applicable to all phases of clinical investigation of medicinal products, medical devices, therapeutic interventions and diagnostics.

3. APPLICABILITY

Principal Investigator (PI), Associate Investigator(s), research coordinators and other staff delegated research/trial-related activities by the PI.

4. PROCEDURE

For investigator initiated trials where Western Health (WH) is also the sponsor, obligations owed to or emanating from sponsor should be interpreted to mean WH.

4.1. Responsibilities

The sponsor, through their independent safety monitoring arrangements, has the primary responsibility for monitoring the ongoing safety of the investigational medicinal product or device. The Human Research Ethics Committee (HREC) should be satisfied that the sponsor's arrangements are sufficiently independent and commensurate with the risk, size and complexity of the trial.

It is the responsibility of Sponsors, Contract Research Organisations, Investigators, Institutions and delegates who are conducting HREC-approved clinical research, together with all Ethics Committee Secretariat staff members to follow and adhere to the procedures set out in this Standard Operating Procedure (SOP).

It is the responsibility of Sponsors, Contract Research Organisations, Investigators, Institutions and delegates who are conducting HREC-approved clinical trials involving therapeutic goods to also comply with the reporting requirements in NHMRC Guidance: Safety monitoring and reporting in clinical trials involving therapeutic goods (2016) (NHMRC Guidance)

4.2. Procedure

When communicating safety information to the HREC, the sponsor or delegate must clarify the impact of each report on patient safety, trial conduct and trial documentation. The items below should be submitted to the reviewing HREC by the sponsor or delegate.

The procedure to be followed is provided in the following table:

Reporting Party	Report Required and Timeline	Supporting Information Required
Sponsor or delegate	Provide the HREC with **annual** update of the **Investigator's Brochure (IB)** or where applicable, **Product Information.** Provide the HREC with any addenda to the **IB** or where applicable, **Product Information**.	Impact of the update/addenda on patient safety, trial conduct and trial documentation.

Sponsor or delegate	Provide the HREC with an **Annual Safety Report** including a clear summary of the evolving safety profile of a trial. NOTE: The HREC 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 Ethical Approval for a trial or may be instituted during the conduct of the trial.	A brief description and analysis of new and relevant findings; For Investigational Medicinal Products (IMPs) not on the Australian Register of Therapeutic Goods a brief analysis of the safety profile of the IMP and implications for participants taking into account all available safety data and results of relevant clinical or non-clinical studies A brief discussion of the implication of the safety data to the trials risk-benefit ratio A description of any measures taken or proposed to minimise risks
Sponsor or delegate	Notify the HREC of all Significant Safety Issues (SSIs) that adversely affect the safety of participants or materially impact on the continued ethical acceptability or conduct of the trial. 1. Significant Safety Issues that meet the definition of an **Urgent Safety Measure (USM)** should be notified **within 72 hours** 2. All other **SSI** should be notified within **15 calendar days** of the sponsor instigating or being made aware of the issue. 3. **SSIs** often result in safety-related changes to trial documentation. Any resulting **amendment** should be submitted to the HREC **without undue delay**. 4. **Temporary halt of trial for safety reasons** should be notified **within 15 calendar days** of the sponsor's decision to halt the trial.	1. Reason for the urgent safety measure; measures taken; further actions planned 2. Details of the significant safety issue; further actions planned 3. Submit amendment to the HREC 4. Reasons for the halt; the scope of the halt (e.g. suspension of recruitment or cessation/interruption of trial treatment); measures taken; further actions planned.

	5. **Early termination of a trial for safety reasons** should be notified without undue delay and **within 15 calendar** days of the sponsor's decision to terminate the trial.	5. Reasons for the early termination; measures taken; further actions planned
HREC	Advise the TGA, investigators and their institutions of any decision to withdraw approval.	Reasons for the withdrawal of approval and date of withdrawal of approval

4.3. TGA Notification and Safety Reporting Requirements

Trial sponsors should refer to the *NHMRC Safety Monitoring and Reporting in Clinical Trials Involving Therapeutic Goods (2016) (NHMRC Guidance)* for safety reporting requirements. The NHMRC guidance addresses the monitoring, collection and reporting of adverse events that occur in clinical trials involving therapeutic goods conducted under the Clinical Trials Notification (CTN) or Clinical Trials Exemption (CTX) schemes. The NHMRC Guidance has aligned with the European Union's Clinical Trial Regulations: Regulation EU No 536/2014.

According to the NHMRC Guidance, it is the trial sponsor that is responsible for reporting to the TGA.

The NHMRC Guidance outlines the trial sponsor's safety reporting responsibilities for CTN and CTX trials. We have provided further information on how the trial sponsor should notify us of all relevant safety reports for CTN and CTX trials in the following tables.

4.3.1 Safety reporting timeframes for CTN and CTX trials

Single case events from Australian sites: Suspected unexpected serious adverse reactions (SUSARS) and Unanticipated serious adverse device effects (USADES)

Individual SUSARs and USADEs from Australian sites must be reported to the TGA. Refer to the NHMRC Guidance for definitions of SUSARs and USADEs.

Even if initial information is limited (i.e. less than the minimum information required for expedited reporting as outlined in the CPMP/ICH/377/95 Guideline for Clinical Safety Data Management: Definitions and Standards for Expedited Reporting) these details should still be forwarded to the TGA pending receipt and provision of further data.

Type of event	Type of good	Report Format	Timeframe
SUSARs from Australian sites only	Medicines and biologicals	• The new Electronic Data Interchange (EDI) functionality, allows sponsors to submit adverse event reports directly from their system to us. Please review the Electronic submission of individual case safety reports link regarding this functionality. If you require assistance in connecting to this service,	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**

		please send email to e2b.reports@tga.gov.au OR • Adverse event reports can be submitted using the new online reporting form. This can be accessed from the Reporting Problems page. You will be able to use your TBS credentials to log in and submit adverse event reports. If you do not have your own, individual login credentials, you will need to contact your organisation's TBS administrator, who can create your user profile. OR • Blue Card or CIOMS form emailed to adr.reports@health.gov.au Please visit Adverse Event Management System (AEMS) for more information about reporting to the TGA.	For all other Australian SUSARs, no later than **15 calendar days** after being made aware of the case
USADEs from Australian	Medical devices	• Medical Device Incident Reporting System OR • Users Medical Device Incident Report Form emailed to iris@health.gov.au	For fatal or life threatening Australian USADEs, 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 USADEs, no later than **15 calendar days** after being made aware

4.3.2 Significant safety issues* and overseas regulatory action

Type of event	Type of good	Report Format	Timeframe
Significant safety issues (SSIs) requiring implementation of USMs	All therapeutic goods	In writing to the Pharmacovigilance and Special Access Branch via email to clinical.trials@health.gov.au	Within **24 hours** (where possible) and in any case, no later than **72 hours** of the measure being taken

Action with respect to safety that has been taken by another country's regulatory agency (relevant to an ongoing clinical trial in Australia)	All therapeutic goods	In writing to the Pharmacovigilance and Special Access Branch via email to clinical.trials@health.gov.au	Without undue delay and no later than **72 hours** of the trial sponsor becoming aware of the action
All other SSIs: Notification of an amendment** Temporary halt of a trial for safety reasons Early termination of a trial for safety reasons	All therapeutic goods	In writing to the Pharmacovigilance and Special Access Branch via email to clinical.trials@health.gov.au	Without undue delay and no later than **15 calendar days** of the trial sponsor becoming aware of the issue or temporary halt or early termination

*SSIs that arise from analysis of overseas reports (relating to a clinical trial in Australia) should be reported to the TGA as per the timeframes above.

** TGA should receive notification that a SSI has occurred but the amendment revising trial documentation **should be submitted to the HREC only**.

Note: A SUSAR or USADE may also meet the definition of an SSI.

4.3.2 Other report types

Type of event	Type of good	Report Format	Timeframe
Other single case adverse events (AEs)	All therapeutic goods	Up to date tabulations or line listings	On TGA's request
Annual safety reports	All therapeutic goods	Development Safety Update Reports (DSURs) or other annual safety reports.	On TGA's request

5. GLOSSARY

Definitions stated in the N*HMRC document Safety monitoring and reporting in clinical trials involving therapeutic goods November 2016* are the governing definitions for Investigation Medicinal Product (IMP) Trials and Investigational Medical Device (IMD) Trials.

Definitions provided below are broader in scope to allow inclusion of clinical research outside the scope of an IMP or IMD trial in this SOP.

For further explanation of any of the definitions consult the *NHMRC document Safety monitoring and reporting in clinical trials involving therapeutic goods November 2016.*

Annual Safety Report

Summary of all new available safety information relevant to a trial that is received over a 12 month period (the Executive Summary of safety information produced for international regulators, such as the Development Safety Update Report (DSUR) may serve as the Annual Safety Report).

Associate Investigator

Any individual member of the clinical trial team designated and supervised by the investigator at a study site to perform critical study-related procedures and/or to make important study-related decisions (e.g., associates, residents, research fellows). Also referred to as “Sub-Investigator”.

Clinical Trials Notification (CTN)

A notification scheme whereby all material relating to the proposed trial, including the trial protocol is submitted directly to the HREC by the researcher at the request of the sponsor. The TGA does not review any data relating to the clinical trial.

The HREC is responsible for assessing the scientific validity of the trial design, the safety and efficacy of the medicine or device and the ethical acceptability of the trial process, and for approval of the trial protocol.

The institution or organisation at which the trial will be conducted, referred to as the 'Approving Authority', gives the final approval for the conduct of the trial at the site, having due regard to advice from the HREC.

CTN trials cannot commence until the trial has been notified to the TGA and the appropriate notification fee paid.

Clinical Trials Exemption (CTX)

An approval process whereby a sponsor submits an application to conduct clinical trials to the TGA for evaluation and comment.

A TGA Delegate decides whether or not to object to the proposed Usage Guidelines for the product. If an objection is raised, trials may not proceed until the objection has been addressed to the Delegate's satisfaction.

If no objection is raised, the sponsor may conduct any number of clinical trials under the CTX application without further assessment by the TGA, provided use of the product in the trials falls within the original approved Usage Guidelines. Each trial conducted must be notified to the TGA.

A sponsor cannot commence a CTX trial until written advice has been received from the TGA regarding the application and approval for the conduct of the trial has been obtained from an ethics committee and the institution at which the trial will be conducted. There are two forms, each reflecting these separate processes (Parts),that must be submitted to TGA by the sponsor.

Part 1 constitutes the formal CTX application. It must be completed by the sponsor of the trial and submitted to TGA with data for evaluation.

Part 2 is used to notify the commencement of each new trial conducted under the CTX as well as new sites in ongoing CTX trials. The Part 2 form must be submitted within 28 days of the commencement of supply of goods under the CTX. There is no fee for notification of trials under the CTX scheme.

Delegate

A person delegated specific but appropriate tasks in relation to the conduct of a clinical trial. Delegation must be evidenced in writing.

Good Clinical Practice (GCP)

A standard for the design, conduct, performance, monitoring, auditing, recording, analyses, and reporting of clinical trials that provides assurance that the data and reported results are credible and accurate, and that the rights, integrity, and confidentiality of trial participants are protected.

Human Research Ethics Committee (HREC)

A body which reviews research proposals involving human participants to ensure that they are ethically acceptable and in accordance with relevant standards and guidelines.

The National Statement requires that all research proposals involving human participants be reviewed and approved by an HREC and sets out the requirements for the composition of an HREC.

Institution

An institution named as a Participating Site on an Ethical Approval issued by the reviewing HREC.

International Conference on Harmonisation (ICH)

International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use is a joint initiative involving both regulators and research-based industry focusing on the technical requirements for medicinal products containing new drugs.

Investigator's Brochure (IB)

The document containing a summary of the clinical and non-clinical data relating to an investigational medicinal product or device that are relevant to the study of the product or device in humans.

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.

Note: This definition includes biologicals used as investigational medicinal products.

Principal Investigator (PI)

An individual responsible for the conduct of a clinical trial at a trial site ensuring that it complies with GCP guidelines. If a trial is conducted by a team of individuals at a trial site, the investigator is the responsible leader of the team and may be called the Principal Investigator. In this instance they may delegate tasks to other team members.

Product Information

The approved Australian summary of the scientific information relevant to the safe and effective use of a prescription medicine. If the conditions of use differ from those authorised, the PI should be supplemented with a summary of relevant clinical and non-clinical data that supports the use of the product in the trial.

Reviewing HREC

The Human Research Ethics Committee (HREC) that issued the Ethical Approval for the project. Under the multisite review system, a NHMRC certified HREC can review and issue ethical approval for a project at multiple sites. These multiple sites will be named in the initial Ethical Approval or be added as an amendment to the initial Ethical Approval. The "reviewing HREC" is responsible for the ongoing monitoring of the project at those sites.

Significant Safety Issue (SSI)

A safety issue that could adversely affect the safety of participants or materially impact on the continues ethical acceptability or conduct of the trial.

Sponsor

An individual, company, institution or organisation which takes responsibility for the initiation, management, and/or financing of a clinical trial.

Standard Operating Procedure (SOP)

Detailed, written instructions to achieve uniformity of the performance of a specific function.

Suspected Unexpected Serious Adverse Reaction (SUSAR)

An adverse reaction that is both serious and unexpected

Therapeutic Goods Administration (TGA)

Australia's regulatory agency for medical drugs and devices.

Unanticipated Serious Adverse Device Effects (USADE)

A SAE for which there is a degree of probability that the event is an adverse effect attributed to the device, and the adverse effect is unanticipated.

Urgent Safety Measure (USM)

A measure required to be taken in order to eliminate an immediate hazard to a participant's health or safety. *Note: This type of significant safety issue can be instigated by either the investigator or sponsor and can be implemented before seeking approval from HREC's or institutions.*

6. REFERENCES

1. Based on VMIA GCP SOP No.009 Version:1.0 Dated 17 September 2007
2. Based on MACH GCP SOP No.009 Version 1.0
3. ICH E6 Guidelines for Good Clinical Practice, section 4.
4. NHMRC Safety Monitoring and Reporting in Clinical Trials Involving Therapeutic Goods (2016)
5. Australian Clinical Trial Handbook – Guidance on conducting clinical trials in Australia using 'unapproved' therapeutic goods version 2.2 (October 2016)
6. NHMRC The National Statement on Ethical Conduct in Human Research (2007 and updates)

7. APPENDICES

Appendix 1: Report Flowchart for Investigational Medicinal Product Trials

Appendix 2:	Report Flowchart for Investigational Medical Device Trials
Appendix 3:	Sponsor reporting of SUSARS and USADES to TGA (for trials conducted under the CTN or CTX schemes)
Appendix 4:	Sponsor reporting of significant safety issues to TGA (for trials conducted under the CTN or CTX schemes)

8. AUTHORS/CONTRIBUTORS

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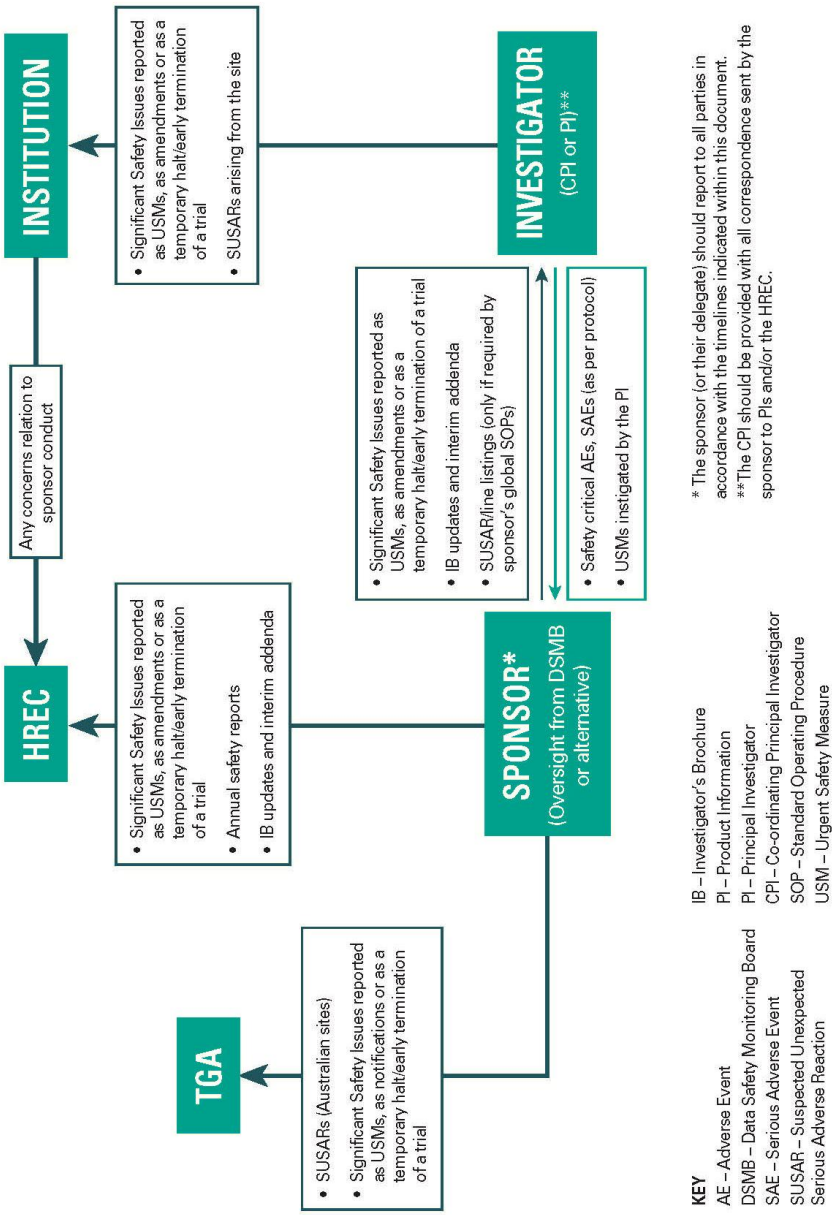
9. PRIMARY PERSON/DEPARTMENT RESPONSBLE FOR DOCUMENT

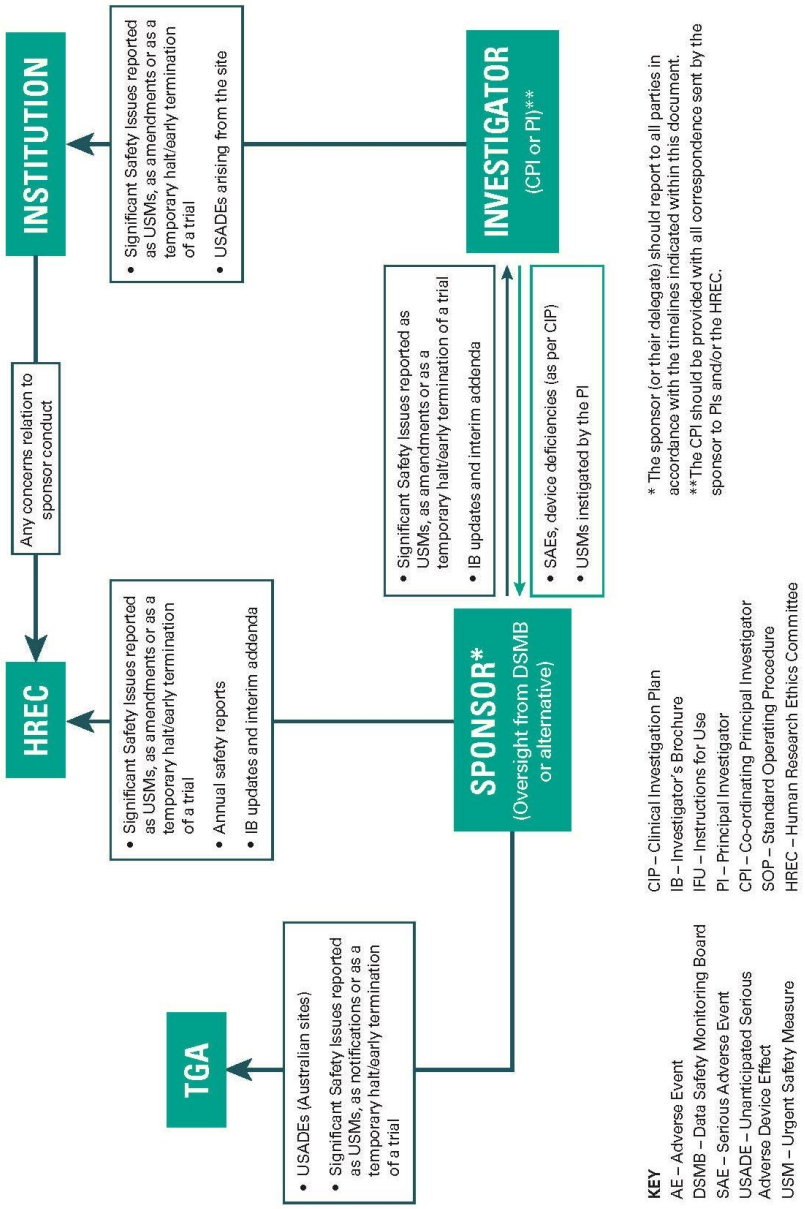
Western Health Office for Research

Appendix 1: Report Flowchart for Investigational Medicinal Product Trials



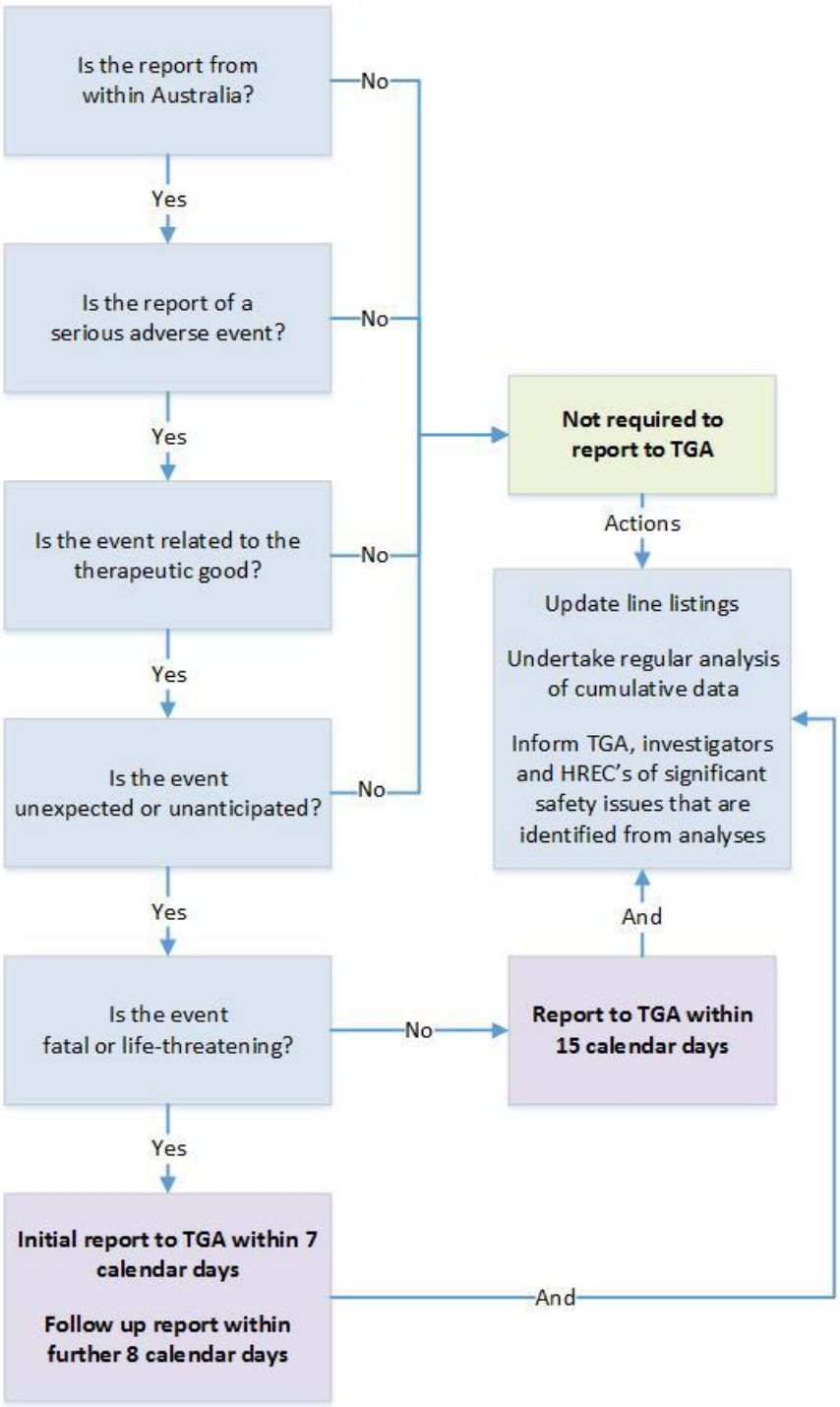
Source: NHMRC document Safety monitoring and reporting in clinical trials involving therapeutic goods November 2016

Appendix 2: Reporting Flowchart for Investigational Medical Device Trials



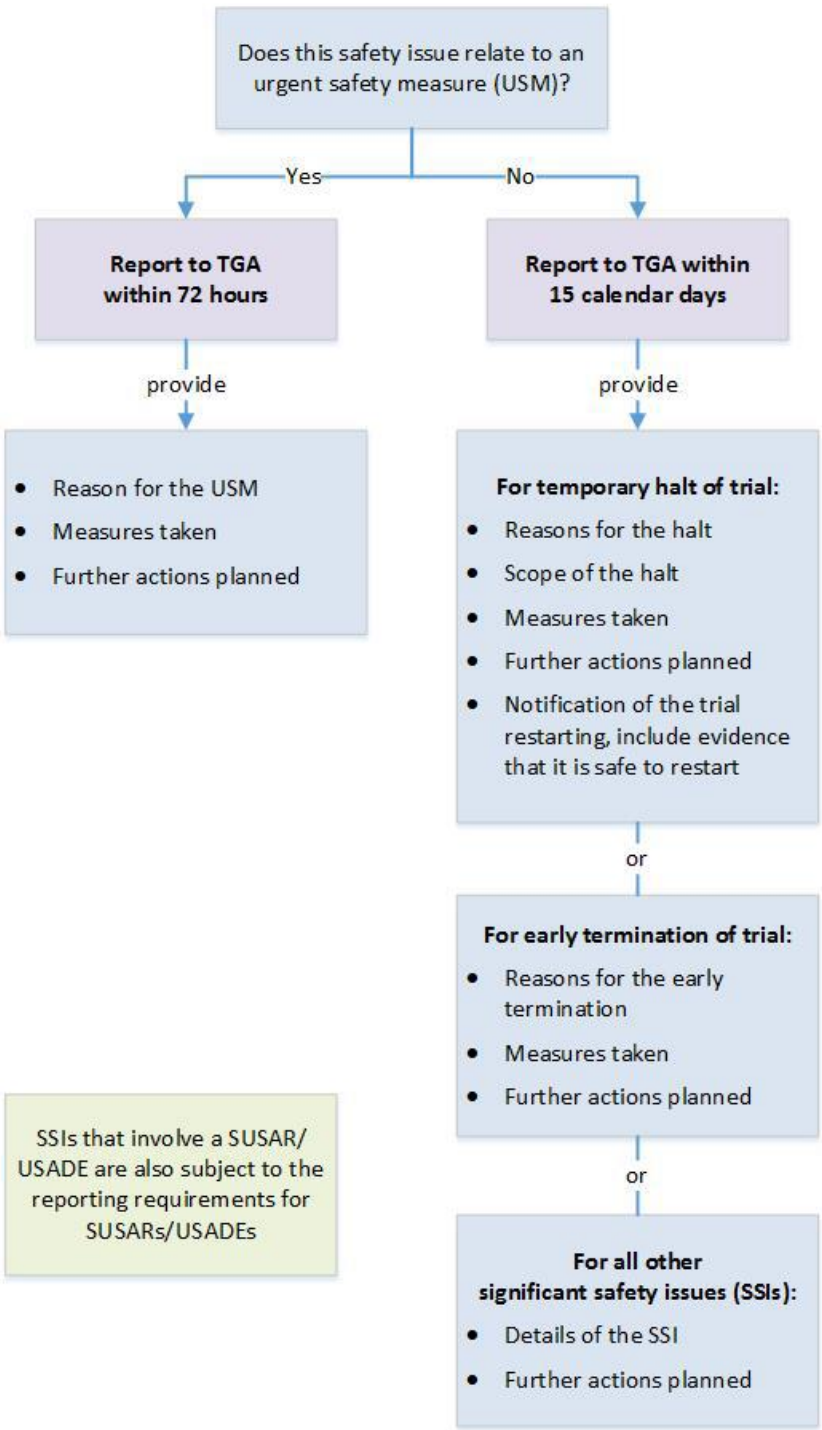
Source: NHMRC document Safety monitoring and reporting in clinical trials involving therapeutic goods November 2016

APPENDIX 3: SPONSOR REPORTING OF SUSARS AND USADES TO TGA (FOR TRIALS CONDUCTED UNDER THE CTN OR CTX SCHEMES)



Source: TGA Australia Clinical Trial Handbook version 2.2 dated October 2018

APPENDIX 4: SPONSOR REPORTING OF SIGNIFICANT SAFETY ISSUES TO TGA (FOR TRIALS CONDUCTED UNDER THE CTN OR CTX SCHEMES)



Source: TGA Australia Clinical Trial Handbook version 2.2 dated October 2018