

<b>DEPARTMENT</b>	Office for Research	
<b>NAME OF DOCUMENT</b>	Monitoring and Reporting of Safety in Clinical Trials Involving Therapeutic Products and Other Clinical Research Guideline	
<b>ISSUE DATE</b>	17 September 2019	
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<b>RESPONSIBLE EXECUTIVE</b>	Angela Watt
<b>PRIMARY AUTHOR</b>	Sarah Rickard
<b>IMPLEMENTATION STRATEGY</b>	Email update to all employees and uploaded to the Office for Research website.
<b>EVALUATION STRATEGY</b>	Updated policy to be evaluated by Melbourne Health Office for Research Governance management team.
<b>STANDARD/S</b> (National, Aged Care, Disability Services)	NSQHS Clinical Governance Standard.
<b>VERSION SUMMARY</b>	These Guidelines for Monitoring and Reporting of Safety for Clinical Trials Involving Therapeutic Products and Other Clinical Research have been developed to clearly set out the roles and responsibilities of Melbourne Health (MH), its Human Research Ethics Committee, investigators and sponsors, and the processes in place in relation to monitoring and reporting reports of adverse events, including serious adverse events (SAEs) and suspected unexpected serious adverse reactions (SUSARs).

These guidelines have been written in accordance with the *National Statement on Ethical Conduct in Human Research (2018)* and the *NHMRC document Safety Monitoring and reporting in clinical trials involving therapeutic products November 2016*.

#### **EXECUTIVE SUMMARY**

1. Appropriate monitoring and safety reporting is a requirement of conducting Clinical Trials Involving Therapeutic Products and Other Clinical Research at Melbourne Health.
2. The Research Governance Officer (RGO) and reviewing HREC must be notified of safety reports as outlined in this guideline.

## **1. ASSOCIATED MELBOURNE HEALTH POLICY**

[MH Research Policy MH18](#)

## **2. PURPOSE AND SCOPE**

The Purpose of these Guidelines is to describe the Melbourne Health (MH) process for monitoring and reporting of safety for clinical trials involving therapeutic products and other Clinical Research, as well as the roles and responsibilities of MH, investigators, the HREC and clinical trial sponsors in relation to monitoring and reporting reports of adverse events.

The HREC has an obligation to ensure that research participants are protected as much as possible and that any changes in the benefit/risk balance of a research study are compatible with continued ethical approval.

Other adverse health outcomes relating to medical practice occurring within MH (and that are unrelated to a clinical trial) are outside the scope of these guidelines.

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### 3. DEFINITIONS

<b>AE</b>	<p>Adverse Event</p> <p>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</p>
<b>AR</b>	<p>Adverse Reaction</p> <p>Any untoward and unintended response to an investigational medicinal product related to any dose administered.</p> <p>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.</p> <p>Note8: The following are examples of types of evidence that would suggest a causal relationship between the investigational product and the adverse event:</p> <ul style="list-style-type: none"> <li>• 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)</li> <li>• One or more occurrences of an event that is not commonly associated with drug exposure, but is otherwise uncommon in the population exposed to the drug (e.g., tendon rupture).</li> <li>• An aggregate analysis of specific events observed in a clinical trial (such as known consequences of the underlying disease or condition under investigation or other events that commonly occur in the study population independent of drug therapy) that indicates those events occur more frequently in the drug treatment group than in a concurrent or historical control group.</li> </ul>
<b>AHEC</b>	Australian Health Ethics Committee ( a principal committee of the NHMRC)
<b>EU</b>	European Union
<b>GCP</b>	Good Clinical Practice as defined in the <i>Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95) – annotated with TGA Comments. DSEB. July 2000<sup>4</sup>.</i>
<b>HREC</b>	Means the Melbourne Health Human Research Ethics Committee
<b>IMP</b>	<p>Investigational Medicinal Product</p> <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>Note: This definition includes biologicals used as investigational medicinal products.</p>
<b>IMD</b>	<p>Investigational Medical Device</p> <p>Medical device being assessed for safety or performance in a clinical investigation</p> <p>Note: This includes medical devices already on the market, that are being evaluated for new intended uses, new populations, new materials or design changes.</p>
<b>MH</b>	Melbourne Health
<b>NHMRC</b>	National Health and Medical Research Council of Australia

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<b>National Statement</b>	National Statement on Ethical Conduct in Human Research 2007
<b>RGO</b>	Research Governance Officer
<b>SAE/SAR</b>	<p>Serious Adverse Event / Serious Adverse Reaction</p> <p>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> <p>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.</p> <p>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.</p>
<b>Safety Critical Adverse Events</b>	Adverse events and/or laboratory abnormalities identified in the protocol as critical to safety evaluations that should be reported to the sponsor according to the reporting requirements specified in the protocol.
<b>SSI</b>	<p>Significant Safety Issue</p> <p>Safety issue that could adversely affect the safety of participants or materially impact on the continued ethical acceptability or conduct of the trial.</p>
<b>SUSAR</b>	<p>Suspected Unexpected Serious Adverse Reaction</p> <p>An adverse reaction that is both serious and unexpected.</p>
<b>TGA</b>	(Australian) Therapeutic Goods Administration
<b>UAR</b>	<p>Unexpected Adverse Reaction</p> <p>An adverse reaction, the nature or severity of which is not consistent with the Reference Safety Information (RSI).</p> <p>Note: The RSI should be contained in the investigator's brochure for an unapproved medicinal product or Product Information (or another country's equivalent of the Product Information) for an approved medicinal product.</p>
<b>USM</b>	<p>Urgent Safety Measure</p> <p>A measure required to be taken in order to eliminate an immediate hazard to a participant's health or safety.</p> <p>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.</p>
<b>SAE</b>	<p>Serious Adverse Event (SAE) -</p> <p>A Serious Adverse Event is defined as any untoward medical occurrence in a clinical trial or other clinical research project that:</p> <ul style="list-style-type: none"> <li>• results in death;</li> <li>• is life-threatening;</li> <li>• requires in-patient hospitalisation or prolongation of existing hospitalisation;</li> </ul>

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	<ul style="list-style-type: none"> <li>• results in a persistent or significant disability/incapacity;</li> <li>• is a congenital anomaly/birth defect; or</li> <li>• is a medically important event or reaction.</li> </ul> <p><i>Source: National Statement on Ethical Conduct in Human Research 2007.</i></p> <p>An event should be considered <b>unexpected</b> if the nature, severity or frequency of that event is not consistent with the information in the Investigator's Brochure if the product or device being trialed is unapproved or if it is not documented in the current Australian Product Information if the product is approved for marketing.</p>
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#### 4. RESPONSIBILITIES

It is the responsibility of Sponsors, Contract Research Organisations, Investigators, Institutions and their delegates, conducting clinical research projects authorised to be conducted at MH to follow and adhere to the procedures set out in this guideline.

It is the responsibility of Sponsors, Contract Research Organisations, Investigators, Institutions and their delegates, conducting clinical trials of therapeutic goods to also comply with the reporting requirements in NHMRC document *Safety Monitoring and reporting in clinical trials involving therapeutic products* November 2016.

It is the responsibility of Investigators and their delegates follow and adhere to the procedures set out in relevant MH policy and procedures.

#### 5. REPORTING REQUIREMENTS

The Research Governance Officer (RGO) and reviewing HREC must be notified of safety reports for a research project, as follows:

Reporting party	Report required and timeline	Supporting information required (IN WRITING)	Follow-up information required (IN WRITING)
<b>Principal Investigator or delegate</b>	<p>Notify the RGO of all Significant Safety Issues <b>occurring at the MH site</b> that adversely affect the safety of participants or materially impact on the continued ethical acceptability or conduct of the trial:</p> <p>I. All <b>Significant Safety Issues occurring at the MH site, including Urgent Safety Measures</b>, should be notified <b>ASAP and within 72 hours</b> of the PI instigating or being made aware of the issue.</p> <p>II. <b>Significant Safety Issues</b> often result in safety-related changes to trial documentation. Any resulting <b>amendment</b> should be submitted to both the reviewing HREC and MH RGO <b>without undue delay</b>.</p> <p>III. <b>Temporary halt of trial for safety reasons at the MH site</b> should be</p>	<p>I. Details of the significant safety issue; reason for the urgent safety measure; measures taken; further actions planned</p> <p>II. Submit amendment per MH Guideline001</p> <p>III. Reasons for the halt; the scope of the halt (e.g.</p>	<p>Submit follow-up information on the reported safety event:</p> <ul style="list-style-type: none"> <li>• Follow-up report when there is a worsening of the event.</li> <li>• Final report when the safety report does not contain the resolution of the event and this information has become available.</li> </ul>

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	notified <b>within 72 hours</b> of the decision to halt the trial.	<i>suspension of recruitment or cessation/interruption of trial treatment); measures taken; further actions planned.</i>	
	IV. <b>Early termination of a trial for safety reasons at the MH site</b> should be notified without undue delay and <b>within 72 hours</b> of the decision to terminate the trial	<i>IV. Reasons for the early termination; measures taken; further actions planned</i>	
<b>Principal Investigator or delegate</b>	Notify the RGO of all <b>SUSARs/USADEs</b> arising at the MH site within <b>72 hours</b>	<i>Details of the event, further actions planned, copy of notification to sponsor</i>	<i>Submit follow-up information on the reported safety event when:</i> <ul style="list-style-type: none"> <li>• <i>There is a worsening of the event.</i></li> <li>• <i>The safety report does not contain the resolution of the event.</i></li> </ul>

These notifications will be acknowledged.

Refer also to the reporting flow charts for Investigational Product trials (Appendix 1) and Investigational Medical Device trials (Appendix 2) from NHMRC document *Safety Monitoring and reporting in clinical trials involving therapeutic products* November 2016.

MH must notify as follows:

<b>Institution</b>	Report any concerns regarding sponsor conduct to the reviewing HREC	<i>Consult HREC for submission advice</i>
	Notify the Victorian Managed Insurance Authority (VMIA) of any SUSARs/USADEs that occur at the MH	<i>Submit per VMIA advice</i>
	Notify the TGA of any	<i>Submit per TGA advice</i>

Refer also to the reporting flow charts for Investigational Product trials (Appendix 1) and Investigational Medical Device trials (Appendix 2) from NHMRC document *Safety Monitoring and reporting in clinical trials involving therapeutic products* November 2016.

## 6. ASSOCIATED POLICIES/PROCEDURES/GUIDELINES

- [MH Research Policy MH18](#)
- [MH Data Management in Research Guideline](#)
- [MH Guidelines for the Use of Human Tissue Samples in Research](#)
- [MH19 Risk Management Policy](#)
- [MH19.02 Incident Reporting](#)
- [MH14.08 Adverse Drug Reaction Documentation and Reporting](#)
- [PCY08.03 Assessing and Processing Reported Adverse Drug Reactions](#)

## 7. REFERENCES

<b>DEPARTMENT</b>	Office for Research	
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- [Australian Code for the Responsible Conduct of Research \(2007updated 2018\)](#)
- [National Statement on Ethical Conduct in Human Research \(2007updated 2018\)](#)
- [Safety monitoring and reporting in clinical trials involving therapeutic goods \(2016\)](#)
- [Therapeutic Goods Act \(1989\)](#)
- [ICH Good Clinical Practice \(GCP\) - Integrated Addendum to ICH E6 \(R1\) Guideline for Good Clinical Practice E6 \(R2\) \(formerly adopted by the TGA with annotations on 8 February 2018\)](#)
- [Guide to Managing and Investigating Potential Breaches of the Australian Code for the Responsible Conduct of Research \(2018\)](#)
- [Management of Data and Information in Research - A guide supporting the Australian Code for the Responsible Conduct of Research](#)

## 8. APPENDICIES

APPENDIX 1: REPORT FLOWCHART FOR INVESTIGATIONAL MEDICINAL PRODUCT TRIALS

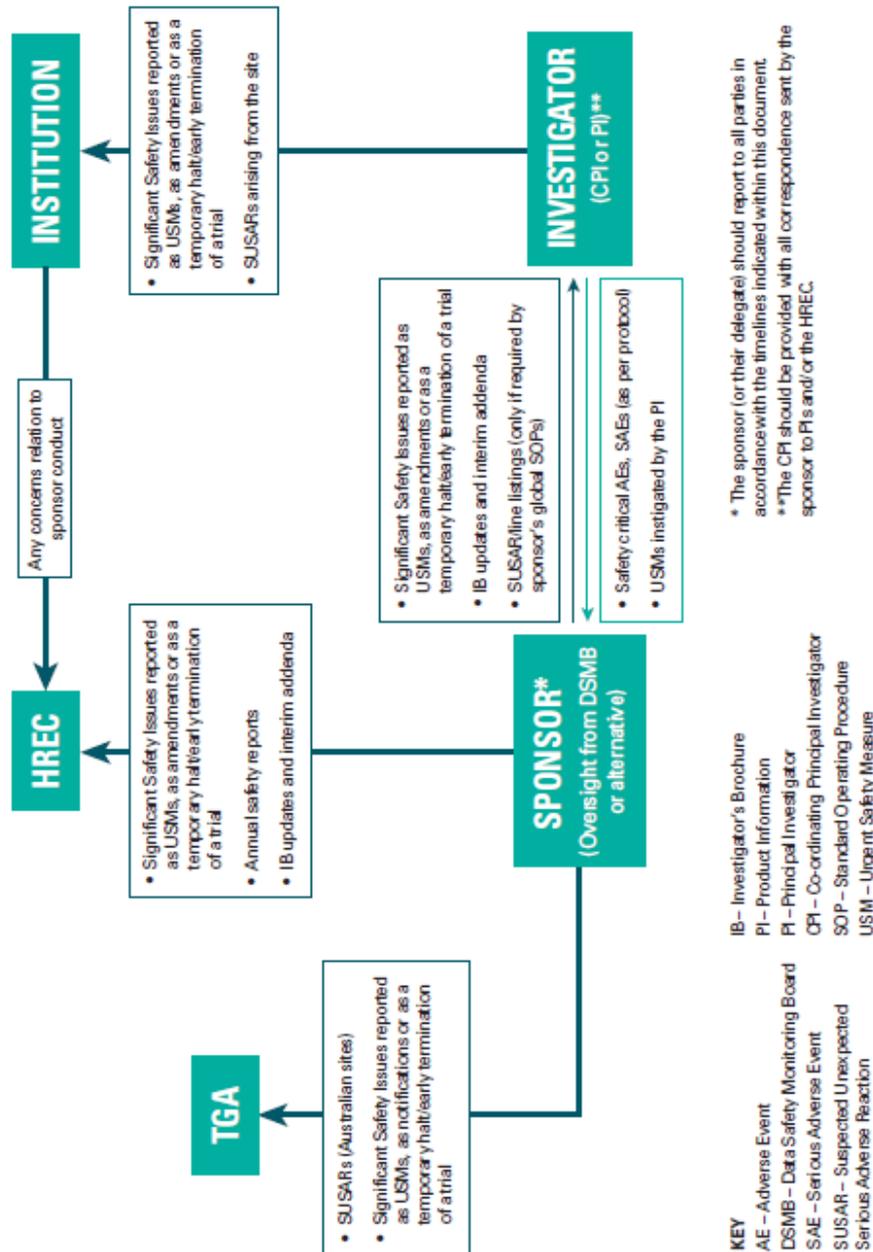
APPENDIX 2: REPORT FLOWCHART FOR INVESTIGATIONAL MEDICAL DEVICE TRIALS

## 9. REVISION AND APPROVAL HISTORY

Date	Version	Author and approval
07/11/2008	1	Angela Watt, Manager Office for Research
17/07/2009	2	Angela Watt, Manager Office for Research
07/06/2010	3	Angela Watt, Manager Office for Research
22/08/2013	4	Angela Watt, Director, Research Governance and Ethics
12/03/2015	5	Jessica Turner, Manager, Human Research Ethics Committee
30/3/2017	6	Sarah Rickard, Manager Research Governance and Audit
17/9/2019	7	Sarah Rickard, Manager Research Governance and Audit

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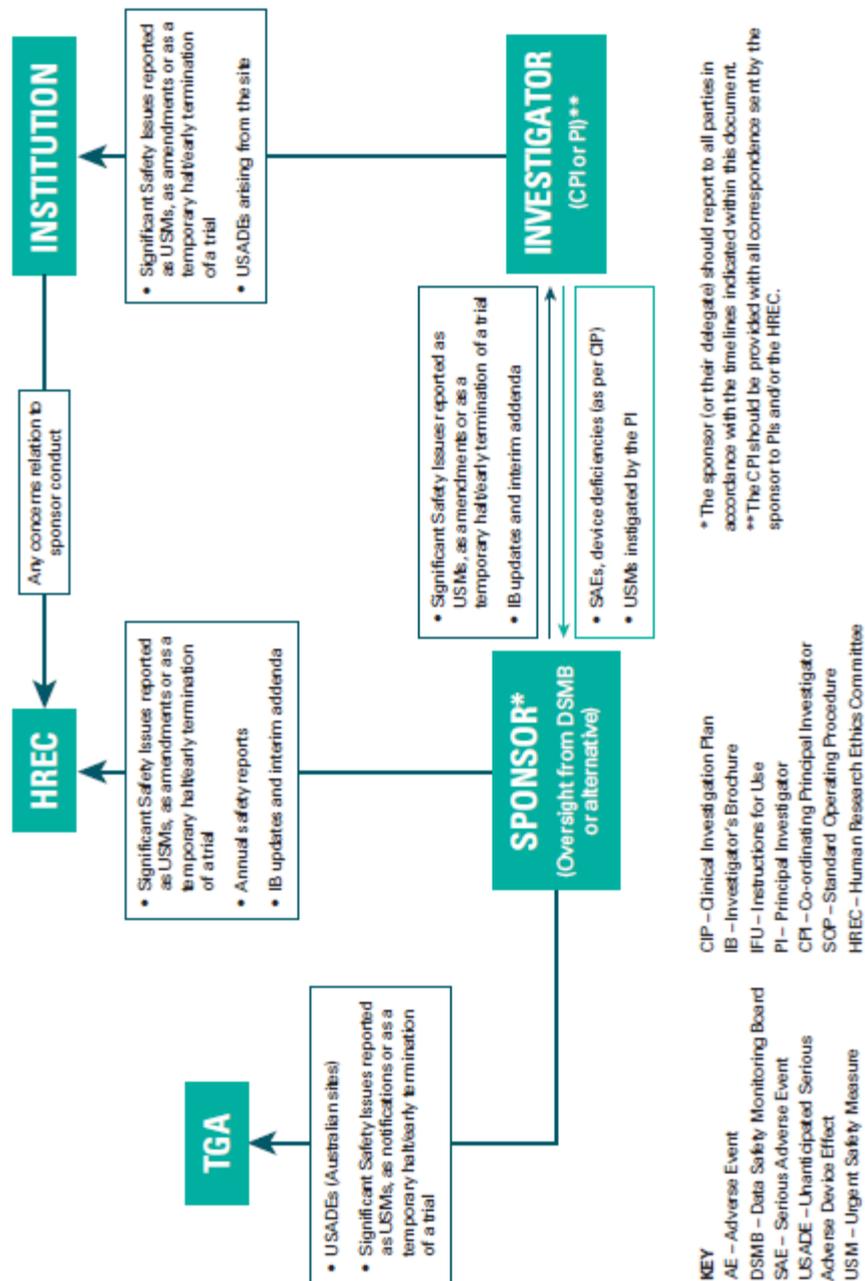
Appendix 1: REPORTING FLOWCHART FOR INVESTIGATIONAL MEDICINAL PRODUCT TRIALS



Flow chart sourced from NHMRC document *Safety Monitoring and reporting in clinical trials involving therapeutic products* November 2016.

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APPENDIX 2: REPORT FLOWCHART FOR INVESTIGATIONAL MEDICAL DEVICE TRIALS



Flow chart sourced from NHMRC document *Safety Monitoring and reporting in clinical trials involving therapeutic products* November 2016