Melbourne Health

Melbourne Health Guidelines Cover Sheet

NAME OF DEPARTMENT	OFFICE FOR RESEARCH
NAME OF DOCUMENT	**Monitoring and Reporting of Safety in Clinical Trials Involving Therapeutic Products and Other Clinical Research**
NUMBER	18.8
ASSOCIATED MELBOURNE HEALTH POLICY	Research Policy[1]
DATE OF ISSUE	30 March 2017
REVISION NUMBER	5.0
FUNCTIONAL GROUP	Research
DIVISIONAL SPONSOR	Executive Director of Research
EQUiP CRITERION 4	Criterion 4: Research Governance The organisation's research program develops the body of knowledge, protects staff and consumers / patients and has processes to appropriately manage the organisational risk 15.10 Fostering and encouraging clinical and health services research. 15.11 Ensuring research integrity through governing body oversight.
SUMMARY	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 (2007)*[3] and the *NHMRC document Safety Monitoring and reporting in clinical trials involving therapeutic products November 2016*[2].

Authorised by: Executive Director of Research

1. ASSOCIATED POLICY

MH18 Research Policy

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

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.

3. DEFINITIONS

AE	Adverse Event 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
AR	Adverse Reaction Any untoward and unintended response to an investigational medicinal product related to any dose administered. 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. Note8: The following are examples of types of evidence that would suggest a causal relationship between the investigational product and the adverse event: • 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) • 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). • 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.
AHEC	Australian Health Ethics Committee (a principal committee of the NHMRC)
EU	European Union
GCP	Good Clinical Practice as defined in the *Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95) – annotated with TGA Comments. DSEB. July 2000*[4]*.*
HREC	Means the Melbourne Health Human Research Ethics Committee
IMP	Investigational Medicinal Product 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.
IMD	Investigational Medical Device Medical device being assessed for safety or performance in a clinical investigation Note: This includes medical devices already on the market, that are being evaluated for new intended uses, new populations, new materials or design changes.
MH	Melbourne Health
NHMRC	National Health and Medical Research Council of Australia
National Statement	National Statement on Ethical Conduct in Human Research 2007
RGO	Research Governance Officer
SAE/SAR	Serious Adverse Event / Serious Adverse Reaction 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. 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. 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.
Safety Critical Adverse Events	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.
SSI	Significant Safety Issue

	Safety issue that could adversely affect the safety of participants or materially impact on the continued ethical acceptability or conduct of the trial.
SUSAR	Suspected Unexpected Serious Adverse Reaction An adverse reaction that is both serious and unexpected.
TGA	(Australian) Therapeutic Goods Administration
UAR	Unexpected Adverse Reaction An adverse reaction, the nature or severity of which is not consistent with the Reference Safety Information (RSI). 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.
USM	Urgent Safety Measure 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 HRECs or institutions.
SAE	Serious Adverse Event (SAE) - A Serious Adverse Event is defined as any untoward medical occurrence in a clinical trial or other clinical research project that: • results in death; • is life-threatening; • requires in-patient hospitalisation or prolongation of existing hospitalisation; • results in a persistent or significant disability/incapacity; • is a congenital anomaly/birth defect; or • is a medically important event or reaction. *Source: National Statement on Ethical Conduct in Human Research 2007.* An event should be considered **unexpected** 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.

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 relate MH policies.

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)
Principal Investigator or delegate	Notify the RGO of all Significant Safety Issues **occurring at the MH site** that adversely affect the safety of participants or materially impact on the continued ethical acceptability or conduct of the trial:	
	I. All **Significant Safety Issues occurring at the MH site, including Urgent Safety Measures,** should be notified **ASAP and within 72 hours** of the PI instigating or being made aware of the issue.	*I. Details of the significant safety issue; reason for the urgent safety measure; measures taken; further actions planned*
	II. **Significant Safety Issues** often result in safety-related changes to trial documentation. Any resulting **amendment** should be submitted to both the reviewing HREC and MH RGO **without undue delay**.	*II. Submit amendment per MH Guideline001*
	III. **Temporary halt of trial for safety reasons at the MH site** should be notified **within 72 hours** of the decision to halt the trial.	*III. 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.*
	IV. **Early termination of a trial for safety reasons at the MH site** should be notified without undue delay and **within 72 hours** of the decision to terminate the trial	*IV. Reasons for the early termination; measures taken; further actions planned*
Principal Investigator or delegate	Notify the RGO of all **SUSARs/USADEs** arising at the MH site within **72 hours**	*Details of the event, further actions planned, copy of notification to sponsor*

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.

6. MH must notify as follows:

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

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.

7. REFERENCES

These guidelines should be read in conjunction with:

1. Melbourne Health Research Policy
2. NHMRC document *Safety Monitoring and reporting in clinical trials involving therapeutic products* November 2016 (https://www.nhmrc.gov.au/guidelines-publications/eh59)
3. The *National Statement on Ethical Conduct in Human Research* (NHMRC 2007) (*National Statement*) (http://www.nhmrc.gov.au/publications/synopses/e72syn.htm)
4. Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95) - annotated with TGA comments. DSEB. July 2000. (https://www.tga.gov.au/publication/note-guidance-good-clinical-practice)
5. Note for Guidance on Clinical Safety Data Management: Definitions and Standards for Expedited Reporting (CPMP/ICH/377/95). Annotated with TGA comments, August 2001 (https://www.tga.gov.au/publication/note-guidance-clinical-safety-data-management-definitions-and-standards-expedited-reporting)
6. Australian requirements and recommendations for pharmacovigilance responsibilities of sponsors of medicines. Australian Government Department of Health. Therapeutic Goods Administration. Nov 2011, amended June 2014. (https://www.tga.gov.au/book/export/html/4585)
7. Access to Unapproved Therapeutic Goods – clinical trials in Australia. Australian Government Department of Health and Ageing. Therapeutic Goods Administration. Oct 2004 (https://www.tga.gov.au/publication/access-unapproved-therapeutic-goods-clinical-trials-australia)
8. Human Research Ethics Committees and the Therapeutic Goods Legislation. Commonwealth Department of Health and Aged Care. Therapeutic Goods Administration. June 2001. (https://www.tga.gov.au/sites/default/files/access-hrec.pdf)
9. VMIA Guidelines for Clinical Trials for Victorian Public Hospitals (https://www.vmia.vic.gov.au/)

8. FURTHER INFORMATION

Contact the MH Office for Research on (03) 9342 8530.

9. APPENDICIES

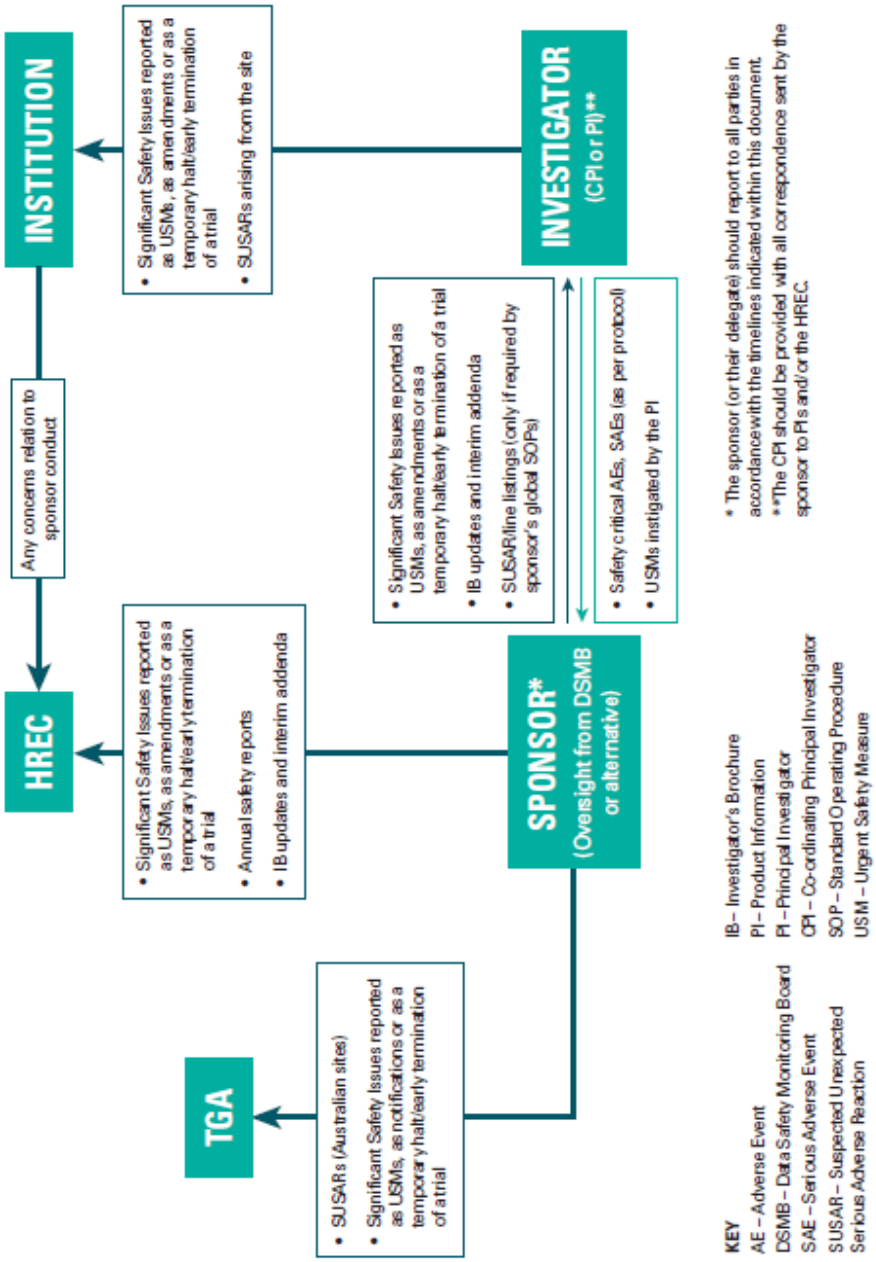
APPENDIX 1: REPORT FLOWCHART FOR INVESTIGATIONAL MEDICINAL PRODUCT TRIALS

APPENDIX 2: REPORT FLOWCHART FOR INVESTIGATIONAL MEDICAL DEVICE TRIALS

10. REVISION AND APPROVAL HISTORY

Date	Rev No	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

Appendix 1: REPORTING FLOWCHART FOR INVESTIGATIONAL MEDICINAL PRODUCT TRIALS



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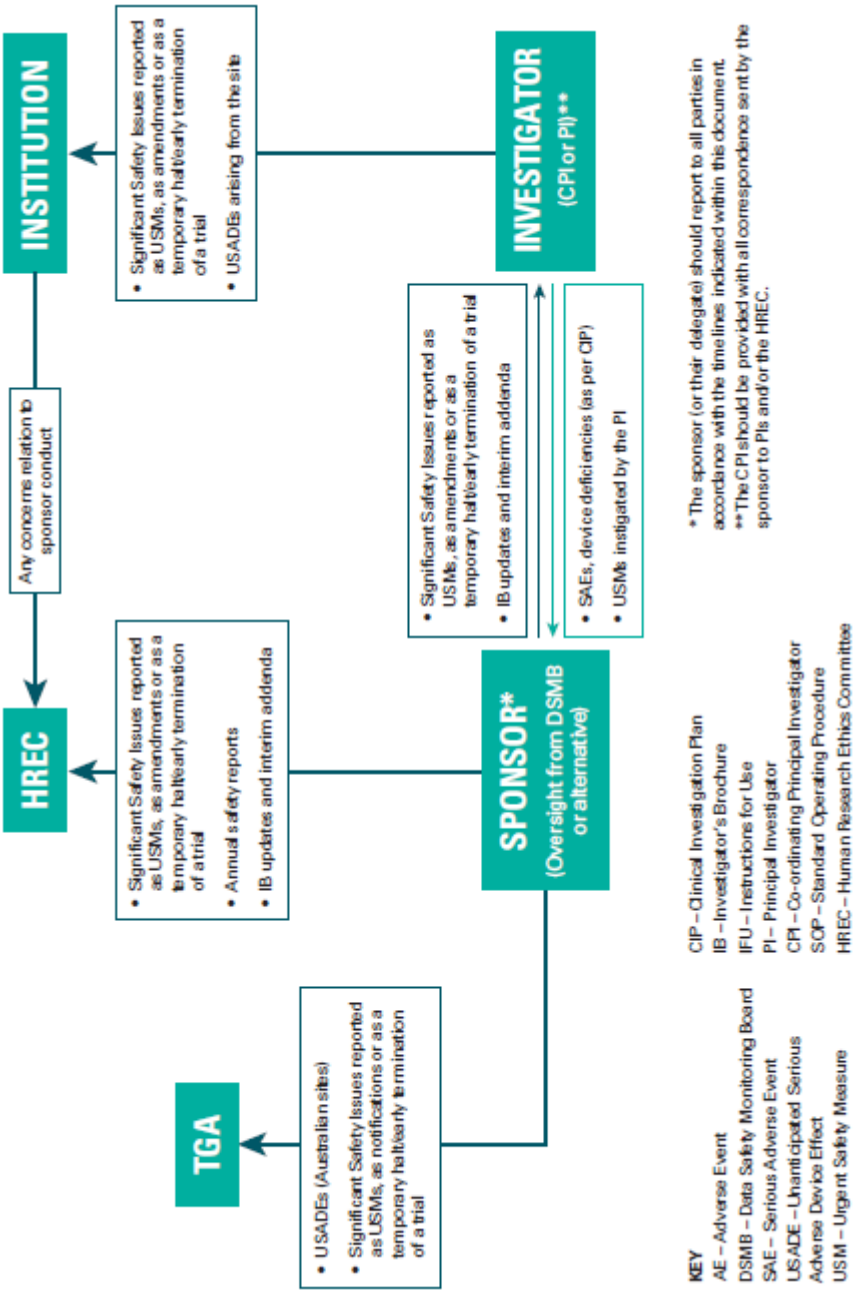
Flow chart sourced from NHMRC document *Safety Monitoring and reporting in clinical trials involving therapeutic products* November 2016.

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