Consultation paper on updating arrangements for safety monitoring and reporting of clinical trials in Australia
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<td>ADE</td>
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<td>AHEC</td>
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<td>IP</td>
<td>Investigational Product</td>
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<td>IRB/IEC</td>
<td>Independent Review Board/Independent Ethics Committee</td>
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<td>ISO</td>
<td>International Organisation of Standardisation</td>
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Executive Summary

The National Health and Medical Research Council (NHMRC) is seeking stakeholders’ views on current practices for safety monitoring and reporting of Serious Adverse Events (SAEs), Adverse Events (AEs), Suspected Unexpected Serious Adverse Reactions (SUSARs), Significant Safety Issues, Urgent Safety Measures and Protocol Violations in Australia and whether international practices could be used to simplify and inform future Australian guidance. In addition, the consultation will seek views on whether there is a need to develop a revised framework for safety monitoring and reporting and, as part of the rolling review of the National Statement on Ethical Conduct in Human Research (2007) (the National Statement), to ensure that any changes arising from this consultation are reflected in the National Statement so that consistent advice is provided for clinical trials in Australia.

Consultation Questions

Stakeholders are invited to submit responses to the following questions.

General

1. Should Australian guidance for safety monitoring and reporting be aligned with International practices? If yes, what key information should be adopted?

2. Do you consider current safety reporting requirements appropriate for (a) Investigators, (b) Institutions, (c) HRECS and (d) Sponsors? If not, how could these be improved?

3. Do current arrangements for safety reporting create any barriers to conducting multi-centre clinical trials? How can these arrangements be streamlined?

Single Case Events

4. What role should the review of single case events play in the monitoring for clinical trials? Are current arrangements appropriate? If not, how should these be changed?

Protocol Violations

5. Should reportable protocol violations be aligned with international practices? If not, what alternatives are suggested?

Significant Safety Issues and Urgent Safety Measures

6. Is more detail on the expedited reporting of significant safety issues and urgent safety measures needed in guidance on reporting? If so, what detail should be included?

Line Listings

7. What role should line listings play in safety monitoring for clinical trials?

Annual Safety Reporting

8. Are the current requirements for annual safety reporting appropriate? If they are considered necessary, what would be the preferred format and content?

9. Is it appropriate for the ICH E2F (Development Safety Update Report) to be accepted as the annual safety report if it has already been produced by a company for international distribution?

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1 This consultation does not extend to the review of TGA guidance.
Expectedness Assessment for Adverse Reactions
10. Would it be beneficial to have guidance on how and why the ‘expectedness assessment’ should be undertaken?

Standardisation of Terminology
11. Is there a need to standardise safety reporting terminology used in Australia? If so, what source(s) should be used to set the standard?

Guidance around Use of DSMBs
12. What further guidance is required for HRECs/sponsors about how DSMBs should operate?

Possible Reporting Arrangements
13. Do the simplified reporting arrangements outlined in Appendix 6 represent an acceptable approach to how safety monitoring and reporting could occur in Australia? If not, what would be an alternative approach?

14. Is it appropriate for safety reporting requirements for medical devices to follow the same systems as those used for investigational products? If not, please outline an alternative approach.

15. Are there any other requirements/considerations that should be implemented for medical device trials that have not been identified by this paper?

Consultation responses should be submitted to Tanya Symons at tsymonsassociates@gmail.com by 6th March 2015.
1. Background

In 2009, the National Health and Medical Research Council (NHMRC) and its principal committee, the Australian Health Ethics Committee (AHEC) published a Position Statement: Monitoring and reporting of safety for clinical trials involving therapeutic products (‘the Position Statement’) to provide guidance on safety monitoring and reporting in clinical trials. This document was intended to clarify the responsibilities of all parties in relation to reports of adverse events, including serious adverse events (SAEs) and suspected unexpected serious adverse reactions (SUSARs) and specified minimum requirements regarding safety reporting in order to comply with the National Statement (Sections 3.3.19-3.3.22 and Section 5.5).

The development of the Position Statement addressed the widely held view by stakeholders that safety reporting in Australia placed too much burden on investigators and Human Research Ethics Committees (HRECs) to comply with requirements that did not genuinely contribute to patient safety. The Position Statement prompted many institutions and HRECs to develop policy on safety monitoring and reporting. However, anecdotal reports suggest that the regulatory burden associated with processing safety reports may have increased without a concomitant increase in patient safety. These increased demands may in part be due to reporting procedures becoming more complex following the introduction of single ethical review in Australia, particularly when the reviewing HREC and institutional staff responsible for the oversight of the clinical trial are not located within the same institution.

Since the release of the Position Statement, both the United States (US) and the European Union (EU) have updated their requirements for safety monitoring and reporting in clinical trials. Both are members of the International Conference on Harmonisation (ICH) which produced the CPMP/ICH/135/95 (ICH GCP) and ICH E2A (Expedited Safety Reporting Guidelines). The Therapeutic Good Administration (TGA) has adopted these guidelines which place the responsibility for the ongoing safety evaluation of the investigational product with the sponsor. The sponsor is also responsible for providing HRECs, investigators and their institutions with timely and appropriate safety information to enable them to perform their roles.

In light of the above changes to international safety monitoring and reporting requirements, the rolling review of the National Statement, and the acceptance of single ethical review for multi-centre human research in Australia, it is now timely to seek stakeholder views on what amendments to the Position Statement and/or the National Statement may be needed to incorporate contemporary guidance on safety monitoring and reporting in clinical trials. As such, NHMRC has engaged a consultant to seek stakeholder feedback on the need for changes to safety monitoring and reporting requirements.

1.1. Purpose and Objectives of this Consultation

The purpose of this consultation is primarily to seek stakeholder views on the need to re-assess the guidance provided in the Position Statement in relation to recent developments in safety monitoring and reporting guidance and policies internationally. In addition, the consultation will seek views on whether there is a need to develop specific guidance to help clarify the roles of key stakeholders and to facilitate a common understanding of all requirements.

1.2. Scope of this Consultation Paper

The Position Statement was developed to specify the minimum requirements for safety reporting in trials involving drugs (investigational products). However, as one of the aims of this consultation is to assess the...
need for a uniform approach to safety monitoring and reporting, this paper also considers the
requirements for trials involving medical devices in Section 6.

1.3. Stakeholder Review and Feedback

The role of sponsors, HRECs, investigators and their institutions are examined. These stakeholders may
wish to provide feedback on all areas, or may prefer to respond only to questions relating to their specific
role. The consultation questions are provided at the beginning of the paper and duplicated throughout,
under the relevant sections of the paper.

Note: This paper makes an assumption that readers have prior knowledge of the safety reporting
definitions and assessments required to determine reportable events. Definitions and flowcharts have
been provided in Appendix 2 and 3.

Questions, feedback and responses to this consultation should be sent to Tanya Symons (T Symons
Associates Pty Ltd): tsymonsassociates@gmail.com by 6th March 2015.

2. Changes to the Clinical Trial Landscape

2.1. Australia

Efforts to streamline ethics review over that last decade are part of major changes to the clinical trials
landscape in Australia. The 2011 report of the Clinical Trials Action Group (CTAG) Clinically competitive:
boosting the business of clinical trials in Australia supported the NHMRC Harmonisation of Multi-centre
Ethical Review (HoMER) initiative and led to the implementation of both the NHMRC’s National Approach
to Single Ethical Review of Multi-centre Research and the multi-state National Mutual Acceptance of single
ethical review. The CTAG report also recommended a number of other improvements to facilitate the
conduct of clinical trials in Australia. These developments have been embraced and extended by initiatives
funded by the previous and current Australian governments which are intended to drive the change
necessary to increase Australia’s competitiveness as a place to conduct clinical trials.

While much work is being done to standardise arrangements for multi-centre clinical trials that have
received a single ethical review, safety monitoring and reporting arrangements have not kept pace with
the changing landscape. Thus, reporting arrangements and requirements remain complex, vary across
States and Territories, and are subject to inconsistent institutional policies and practices.

2.2. Internationally

Since 2009, safety monitoring and reporting requirements have been clarified and simplified with both the
US and EU making amendments to their safety reporting guidance to reflect the ‘current thinking’ of their
regulatory agencies.

In the US, the Code of Federal Regulations (21 CFR part 312, 32 & 33) describes the safety reporting
requirements. In 2010, the Food and Drugs Administration (FDA) published a final rule amending and
clarifying safety reporting definitions under 21 CFR part 312. Two new guidance documents5 6 that
represent the FDA’s current thinking on the topic of safety reporting, inform this paper. The European
Clinical Trials Directive 2001/20/EC defines safety reporting requirements for clinical trials in all European
Member States. However, this Directive is being repealed and will be replaced by the EU Clinical Trials
Regulation in 2016. Both current and future legislation inform this paper.

5 Safety Reporting for INDs and BA/BE Studies 2012
6 Safety Reporting for INDs and BA/BE Studies 2012 – Small Entity Compliance Guide
3. Summary of Current Safety Reporting Arrangements

In the section below, the US and EU legislation is compared to current Australian arrangements.

The current Australian arrangements for Safety Monitoring and Reporting are outlined in Appendix 4 and 5. These arrangements are complex and vary across States and Territories. Requirements for safety monitoring and reporting for clinical trials are articulated in a number of documents:

1. The National Statement outlines requirements in Sections 3.3.19-3.3.22 and Section 5.5.
2. The Position Statement outlines roles and responsibilities for the reporting of adverse events in order to meet the minimum requirements of the National Statement.
3. The Monitoring Tables provide information on the safety reporting requirements for multi-centre clinical trials in each State and Territory.

The tables in Appendix 1 summarise the requirements for safety reporting by sponsors to regulatory authorities, investigators and ethics committees in the US and EU and enable a comparison of each system with the Position Statement. The section below, examines the current responsibilities of key stakeholders, and compares these with international practices.

3.1. Investigator Responsibilities

3.1.1. Australia

a. National Statement: The National Statement (Section 3.3.22 (d) and (e)) outlines the responsibilities of researchers in relation to safety reporting:

“(d) notifies (to the HREC) in the manner and form specified by the HREC, any serious adverse events at any of those trials sites and (e) informs the HREC as soon as possible of any new safety information from other published or unpublished studies that may have an impact on the continued ethical acceptability of the trial or may indicate the need for amendments to the trial protocol”.

b. Position Statement: The Position Statement outlines the following responsibilities:

“The investigator/researcher must capture and report AEs, including SAEs, which occur at their site to the sponsor in accordance with the study protocol.

The investigator/researcher must report all SAEs to the sponsor immediately (within 24 hours) in accordance with the study protocol and GCP guidelines as adopted by the TGA”

The investigator must provide the following for each trial:

- “In accordance with individual institutional requirements to institution (or HREC as specified by institution) AEs or SAEs occurring at their site(s)

- In a prompt manner to HREC responsible for trial:

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7 It is important to highlight that ICH GCP Section 3: Ethics Committee Responsibilities has not been adopted in Australia. Most countries place the responsibility for the trial’s initial assessment of risks and benefits with their Regulatory Authority. The TGA has adopted a risk-adapted approach and has placed the responsibility for the review of the scientific validity of the trial design and the safety and efficacy of the investigational product during trial approval, with the HREC. The TGA has not altered the responsibility for the ongoing assessment of the safety of the investigational product, which lies with the trial sponsor.
information which materially impacts the continued ethical acceptability of the trial or
information that requires, or indicates the need for, a change to the trial protocol, including changed safety monitoring in the view of the investigator or sponsor.

• At least six-monthly to HREC responsible for trial:
  o listing of all SUSARs, Australian and international, occurring with a compound
  o including sponsor and investigator comment as to whether action is planned for the trial on the basis of the reports
  o EU format is acceptable.

• At least annually to HREC responsible for trial:
  o an updated Investigator Brochure, or
  o an EU ASR (or similar format report), or
  o current, approved Product Information (PI), if appropriate (e.g. in a study for a product approved in Australia or where an Investigator Brochure is no longer maintained)
  o other reports consistent with Section 5.5.5 of the National Statement1 and Good Clinical Practice (GCP) as adopted by the Therapeutic Goods Administration (TGA).”

In addition, the Position Statement requires investigators to, “comment whether action is planned for the trial on the basis of the reports.”

At present in Australia, the practice of reporting AEs and SAEs to HRECs and institutions still appears to be widespread even though the Position Statement suggests that institutions should; “keep these requirements to a minimum”. This recommendation was added to the Position Statement because in general, single case adverse events are not informative without a comparison of the incidence in treated/untreated groups (an aggregate assessment by the sponsor). With only a few exceptions8, in the absence of the sponsor’s aggregate assessment which will only be conducted at intervals, it is difficult for investigators, (or HRECs and institution’s governance staff) to make immediate judgments on whether a single event has any impact on the continued ethical acceptability or conduct of a trial.

c. Monitoring Tables: These provide information on the reporting requirements for multi-centre clinical trials taking place in States and Territories. These tables require local Principal Investigators to make immediate judgments on whether all single events have any impact on the continued ethical acceptability of the trial, before reporting to the HREC. A summary of the requirement from the monitoring tables including the roles of investigators (CPI and PI) are shown in Appendix 4.

d. TGA Requirements: The TGA outline their expectations for investigators in guidance documents including ‘The Australian Clinical Trials Handbook (2006)’ which reiterates the requirements outlined in ICH GCP. Section 4.11 of ICH GCP states:

“All serious adverse events (SAEs) should be reported immediately to the sponsor except for those SAEs that the protocol or other document (e.g., Investigator’s Brochure) identifies as not needing immediate reporting. The immediate reports should be followed promptly by detailed, written reports. The immediate and follow-up reports should identify subjects by unique code numbers assigned to the trial subjects rather than by the subjects’ names, personal identification numbers, and/or addresses. The investigator should also comply with the applicable regulatory requirement(s) related to the reporting of unexpected serious adverse drug reactions to the regulatory authority(ies) and the IRB/IEC.

8 Exceptions where single events may be deemed causally related in the absence of any aggregate assessment (and therefore may be informative) are outlined on page 4 of the Safety Reporting Requirements for INDs and BA/BE Studies
Adverse events and/or laboratory abnormalities identified in the protocol as critical to safety evaluations should be reported to the sponsor according to the reporting requirements and within the time periods specified by the sponsor in the protocol.

For reported deaths, the investigator should supply the sponsor and the IRB/IEC with any additional requested information (e.g., autopsy reports and terminal medical reports)."

ICH GCP also states that investigators "...should ensure that adequate medical care is provided to a subject for any adverse events". As such, investigators should review all adverse events, both serious and non-serious and act as clinical care dictates. However, the investigator’s review of safety reports may not have the same scope, breadth of information and perspective as the sponsor’s review. It is for this reason that the investigator is required to provide the sponsor with all relevant information so that the sponsor can perform the overarching analysis and report any significant findings to relevant bodies.

3.1.2. Internationally

International guidance in both EU and US aligns with Section 4.11 of ICH GCP for investigator reporting responsibilities.

With regard to the role of the investigator in reviewing reports to determine whether action is planned for the trial, the following extract from FDA Guidance (Safety Reporting for INDs and BA/BE Studies 2012) clarifies the FDA’s (and the EU’s) view on the evaluation of individual case serious adverse experiences for which there is little reason to believe that the drug caused the event (i.e. SAEs as defined in 3.3.20b)(i) of the National Statement):

“These types of reports... do not contribute meaningfully to the developing safety profile of an investigational drug or to human subject protection. Attempting to review and evaluate these reports without the necessary context was also a drain on resources for FDA, investigators, and institutional review boards (IRBs), diverting them from other activities.”

3.2. Institutional Responsibilities

3.2.1. Australia

a. National Statement:

Section 5.5.1 states:

“Each institution has ultimate responsibility for ensuring, via its research governance arrangements, that all its approved research is monitored”.

Section 3.3.19 states:

“The ultimate responsibilities of institutions for monitoring the conduct of approved research are described in Chapter 5.5: Monitoring approved research. In clinical research, and especially clinical trials, research sponsors also have such responsibilities.”

Section 3.3.20 expands on the institutions responsibilities:

“Institutions responsible for the conduct of clinical research should require that:

a) monitoring arrangements are commensurate with the risk, size and complexity of the trial;
b) for each project, there are mechanisms for reporting and reviewing:

(i) serious adverse events at any site for which the institution is responsible;
(ii) serious adverse drug reactions (ADRs), serious unexpected suspected adverse reactions (SUSARs), and serious adverse device events from any site for which the institution is responsible;

c) for a large multi-centre trial, a Data and Safety Monitoring Board (DSMB) is used and there is a mechanism for informing the HREC of any relevant emerging data from the DSMB;

d) for a local trial, there is an identified person/s or committee with suitable expertise to assist and advise the HREC about reports of serious adverse events.”

b. Position Statement: The Position Statement outlines the expectations with regard to reporting requirements stating that institutions should receive AEs and SAEs, “in accordance with individual institutional requirements”.

c. Monitoring Tables: These tables do not prescribe a specific role for the institution. With regard to safety reporting, as the Position Statement allows each institution to define their specific requirements, the Monitoring Tables reflect the considerable variation that has evolved across States and Territories.

d. TGA Requirements: The TGA recognises that the institution provides the infrastructure which enables the investigator to conduct the trial.

3.2.2. Internationally

The US Code of Federal Regulations 21CFR 312 and The EU Directive 2001/20/EC do not contain significant information on the role of the institution. However, there is a clear expectation from GCP inspectors that institutions have oversight\(^9\) of all clinical trials that are conducted on their premises. When an institution is also taking on the role of sponsor, they are then also responsible for monitoring the trial (ICH GCP Section 5.18) which may include checks to confirm whether investigators are complying with safety reporting requirements.

The UK model, outlined below, describes the safety reporting expectations for institutions that either ‘host’ externally sponsored trials or ‘sponsor’ their own non-commercial trials:

- **For externally sponsored trials with a local Principal Investigator:** Institutions do not routinely request local AEs or SAEs but do request local SUSARs. SUSARs are collected not for the purposes of assessment, but so that institutions are kept informed of any issues that may require management, such as disputes or litigation resulting from trials. As with HRECs, institutions satisfy themselves that sponsors have adequate arrangements in place for ongoing safety monitoring. They also ensure sponsors are aware that they must promptly report anything that may impact on the trial’s continued site authorisation.

  All hospitals operate clinical incident reporting systems so that reported information can be used to make changes to improve patient care. The UK’s Regulatory Agency, the MHRA have recommended that these systems also capture any research-related events that meet the definition of a clinical incident.

- **For trials sponsored by the institution with a local Coordinating Principal Investigator (CPI):** The MHRA expect the ‘UK sponsor-institution’ to have developed a trial risk assessment process to ensure that appropriate and proportionate measures are in place to monitor the safety of participants. Where the CPI takes on some or all of the sponsor’s responsibilities, the MHRA also expect the institution to have close oversight of the CPI’s safety monitoring systems to ensure

\(^9\) The term ‘monitoring’ is not used internationally in this context as it has a specific meaning in ICH GCP 5.18.1 and refers to the activities that sponsors must undertake.
compliance with all regulatory requirements. Unless the institution has a robust and tested pharmacovigilance system, there is usually an expectation that the sponsor’s responsibilities for pharmacovigilance are outsourced or delegated to appropriate bodies for all but the simplest of trials. Institution’s governance staff do not routinely collect AEs or SAEs, as the ongoing safety evaluation of a trial is usually delegated to individuals/bodies with the appropriate qualifications and training. SUSARs are collected ‘for information’, as described above.

3.3. HREC Responsibilities

3.3.1. Australia

a. National Statement: The National Statement (Section 3.3.21) outlines the responsibilities of HRECs in relation to safety monitoring:

“HRECs should review approved projects in light of information provided to them (by the institution/investigator) under paragraph 3.3.20.”

In addition, Section 3.3.20 states:

Institutions responsible for the conduct of clinical research should require that:
(a) monitoring arrangements are commensurate with the risk, size and complexity of the trial;

(b) for each project, there are mechanisms for reporting and reviewing: (i) serious adverse events at any site for which the institution is responsible; (ii) serious adverse drug reactions (ADRs), serious unexpected suspected adverse reactions (SUSARs), and serious adverse device events from any site for which the institution is responsible;

(c) for a large multi-centre trial, a Data and Safety Monitoring Board (DSMB) is used and there is a mechanism for informing the HREC of any relevant emerging data from the DSMB; (d) for a local trial, there is an identified person/s or committee with suitable expertise to assist and advise the HREC about reports of serious adverse events.

b. Position Statement: The Position Statement states that HRECs:

“be aware of the proposed monitoring arrangements as part of the approval process, and should be satisfied, that through the collaboration of the institution, sponsor and investigators that those processes are commensurate with the risk, size and complexity of the proposed research”.

The Position Statement outlines a number of possible approaches to monitoring safety in clinical trials including:

- a pharmacovigilance group in a company-sponsored clinical trial
- a trial management committee
- a data safety monitoring board
- a simpler but separate review process for investigator or collaborative sponsored trials

It also suggests the HREC, “Conduct review of safety information within the HREC if the HREC has sufficient resources and expertise.”

c. Monitoring Tables: These tables require HRECs to receive and review safety reports from either the CPI or PI. The HREC has responsibility to notify the CPI/PI of its decision within a specified timeframe (which can vary from 5-14 calendar days) for each State and Territory.
d. **TGA Requirements**: The TGA’s ‘Access to Unapproved Therapeutic Goods’ states that adverse reactions/events are reported to the HREC, “as required by the HREC”.

### 3.3.2. Internationally

Responsibilities for HRECs relating to receipt of safety information are outlined in Section 3.3.8 of ICH GCP. The UK’s National Research Ethics Service has produced guidance to research ethics committees (RECs) relating to their role in safety assessment:

> “The REC will receive some interim data about clinical trials in progress reports, annual safety reports and expedited safety reports, including any suspected unexpected serious adverse reactions and unanticipated serious adverse device events (SUSARs/USADEs). However, the REC may not be best placed to perform an analysis using this data. As a voluntary body it may not have the resources and expertise to undertake in-depth monitoring and the data it receives are partial. It therefore relies on assurances from the sponsor that it has adequate arrangements* in place for monitoring the safety of a clinical trial.”

*Note: The requirement for the HREC to satisfy itself that the sponsor has ‘adequate arrangements’, is particularly important for non-commercial trials that do not have the support of pharmacovigilance departments.

Ethics committees in New Zealand no longer wish to receive SAEs/SUSARs (see p 44-46 of New Zealand’s Health and Disability Ethics Committee SOPs).

In both the US and EU, sponsors are permitted to send SUSARs directly to the ethics committee. In addition, the US and EU systems appear to be less burdensome for HRECs as they are not required to process AEs and SAEs or six monthly line listings. Single case SUSARs are expedited to HRECs in the US and EU at present, but the EU will not mandate this from 2016.

### 3.4. Sponsor Responsibilities

#### 3.4.1. Australia

**a. National Statement**: As the National Statement is designed primarily to clarify the responsibilities of institutions, researchers and ethical review bodies, it does not specify requirements for sponsors. Requirements for sponsors are detailed in the Position Statement.

**b. Position Statement**: The Position Statement describes the requirement for sponsors:

> “In a prompt manner, sponsors must communicate to investigators information which adversely affect the safety of subjects, materially impact the continued ethical acceptability of the trial or that requires (or indicates the need for) a change to the trial protocol, including changed safety monitoring.”

The Position Statement also states that sponsors should:

- establish safety monitoring processes that are commensurate with the risk, size and complexity of the proposed research (which may include establishing a DSMB)
- be in regular communication with the investigators
- keep investigators up to date with safety issues in a trial in a manner that is consistent with the risk, size and complexity of the proposed research
- provide to investigators required periodic information to facilitate investigator submission to the relevant HREC.
Sponsors are responsible for reporting individual case safety reports to the TGA in accordance with expedited reporting guidelines. In investigator-led or collaborative group sponsored studies, responsibility for reporting adverse reactions to the TGA rests with the investigator or collaborative group.

Note: The Position Statement generally discourages the sending of individual SUSARs from Australian or international sites to investigators (and therefore HRECs) unless there is a need due to the risk, size or complexity of the trial. This aligns with current thinking in Europe which does not require SUSARs to be expedited to investigators, and also with 2016 EU legislation, which does not mandate their reporting to ethics committees. It should also be noted that Section 5.17.1 of ICH GCP only obliges SUSARs to be expedited to ethics committees (IECs/IRBs) “where required”.

c. Monitoring Tables: These tables require sponsors to receive safety reports (the type varies across States and Territories) from the PI or CPI and submit these reports to the TGA. Appendix 4 provides detail.

d. TGA Requirements: All SUSARs must also be expedited by the sponsor to the TGA (within seven days for fatal and life threatening SUSARs and fifteen days for all other SUSARs). The TGA also requests, “any significant safety issue which has arisen from an analysis of overseas reports or action with respect to safety which has been taken by another country’s regulatory agency”, to be reported within 72 hours. All other events received by the sponsor should be tabulated and produced on request to the TGA.

3.4.2. Internationally

In both the US and the EU, the sponsor’s responsibilities for safety monitoring are guided by Section 5.16 of ICH GCP and, as described earlier, include the ongoing safety evaluation of the investigational product(s). Many guidance documents also describe the sponsor’s responsibility to have processes for reviewing, evaluating and managing all the accumulating safety data available to them.

With regard to safety reporting, there is a difference in requirements between the US and EU concerning expedited reports of SUSARs. The US require expedited reporting to all investigators whereas the EU stipulate SUSARs should be sent as line listings in periods warranted by the protocol. As such, a company’s safety reporting standard operating procedures (SOPs) will often be guided by the location of their head office as companies will be required to align with either US or EU law.

Where companies are following US (FDA) requirements and are obliged to send SUSARs to investigators, they should be accepted and reviewed in accordance to the sponsor’s procedures. Further consultation is required with industry to determine the nature and scope of these requirements.

Note: In the UK, ethics committees have been provided with national guidance which describes how to handle reports that are sent to them, but are not required under UK law.

3.5. Expedited Reporting of Significant Safety Issues, Urgent Safety Measures and Protocol Violations

In addition to the reporting of SAEs and SUSARs, there are a number of other mechanisms that can be used to expedite safety information or concerns and which are considered here. The first two mechanisms: significant safety issues; and urgent safety measures are already, to some extent, integrated into Australian requirements. However, for a third mechanism: protocol violations, there are differences between Australian and international requirements which are described in Section 4.1.3.
3.5.1. Significant Safety Issues

These are issues that may adversely affect the safety of participants, materially impact on the continued ethical acceptability of the trial or require a change to the trial protocol, including changed safety monitoring. Examples include:

- a significant hazard to the patient population such as lack of efficacy of an investigational product (IP) used for the treatment of a life-threatening disease
- a major safety finding from a newly completed animal study (such as carcinogenicity)
- a temporary halt of a trial for safety reasons if the trial is conducted with the same investigational products in another country by the same sponsor
- recommendations of the Data Safety & Monitoring Board (DSMB), where relevant for the safety of participants

Because these events do not meet the definition of a SUSAR, they are often communicated through the reporting of an urgent safety measure, substantial amendment or the premature termination or temporary halt of a trial.

3.5.2. Urgent Safety Measures

Urgent safety measures are any measures necessary to protect a participant from an immediate hazard. The term ‘urgent safety measure’ is not used universally across Australia but has been adopted in some state and institutional guidance. The requirement to report to the HREC, is described in Section 4.5.4 of ICH GCP and also the TGA’s Australian Clinical Trial Handbook. This type of measure can be instigated by either the investigator or sponsor and can be implemented before seeking approval from HRECs or institutions. They are reported, post hoc as a substantial amendment outlining the measure taken.

3.5.3. Protocol Violations

The expedited reporting of protocol violations provides sponsors with timely information relating to the compliance of sites and also whether their protocols are workable and often prompt the implementation of corrective measures. The expedited reporting of substantial protocol violations to HRECs and institutions allows approval bodies to assess whether appropriate action has been taken in response to the violation and also to take the information regarding protocol violations into account when assessing future applications. The divergence between Australian and international requirements with respect to protocol violations is described below:

3.5.3.1. Australia

a. National Statement: There are no specific references to protocol violations but 3.3.23 states:

   “It may be unethical for a researcher to continue a trial if: (a) there are or have been substantial deviations from the trial protocol”

b. Position Statement: No specific reference to protocol violations

c. Monitoring Tables: The tables indicate that most States and Territories require all protocol deviation and violations to be sent by the investigator to the HREC and institution (although precise requirements differ).

d. TGA Requirements: TGA’s ‘Access to Unapproved Therapeutic Goods’ states:

   “Circumstances that may lead to withdrawal of support for a trial are most likely to arise as a result of the monitoring process. These include: evidence of significant deviation from the trial protocol and that, as a result, the welfare and rights of participants are not or will not be protected”
3.5.3.2. Internationally: ICH GCP states:

“The investigator should not implement any deviation from, or changes of the protocol without agreement by the sponsor and prior review and documented approval/favourable opinion from the IRB/IEC of an amendment, except where necessary to eliminate an immediate hazard(s) to trial subjects, or when the change(s) involves only logistical or administrative aspects of the trial (e.g., change in monitor(s), change of telephone number(s)). The sponsor must ensure that all protocol deviations and violations are documented by the investigator”

This statement clarifies that investigators must work to the protocol unless they are compelled to deviate to protect a patient from an immediate hazard (i.e. are required to implement an urgent safety measure). All other changes must be submitted by the sponsor as a substantial amendment. ICH GCP does not require all deviations and violations to be sent to directly to HRECs but instead, sponsors collect information on all non-compliances during the monitoring process and determine whether any deviation/violation has affected the safety of the participant or the integrity of the data.

There is no internationally accepted definition of the terms protocol deviation or protocol violation. However, with respect to the safety of participants, there is consensus on requirements for reporting to sponsors and approval bodies. For example, both the current and 2016 European Regulation, define reportable protocol violations in terms of a ‘Serious Breach of Good Clinical Practice (GCP) or the Protocol’.

Serious Breach of GCP/Protocol (definition taken from UK Statutory Instrument 1928/2006):

“A breach likely to effect to a significant degree:

a) The safety or physical or mental integrity of the trial participant
b) The scientific value of the trial”

These are reported by investigators to sponsors (or detected by the sponsor during monitoring) who then report on to HRECs and institutions within seven days.

4. Periodic Safety Reporting

4.1. Six Monthly Line Listings

4.1.1. Australian Requirements

In Australia, there is no legislative requirement for periodic line listings for clinical trials. The manufacturers of certain registered medicines must produce Periodic Safety Update Reports as described in the Australian Requirements and Recommendations for Pharmacovigilance Responsibilities (amended June 2014). However, Section 2.5.1 confirms that clinical trials reporting should be in line with TGA clinical trial guidance.

4.1.2. International Requirements

Section 5.17.3 of ICH GCP states; “The sponsor should submit to the regulatory authority(ies) all safety updates and periodic reports, as required by applicable regulatory requirement(s).”

As in Australia, manufacturers of drugs are required to submit Periodic Update Safety Reports to Regulators as part of their responsibilities as Marketing Authorisation Holders. These reports include safety reports from clinical trials but are not required as a reporting requirement for clinical trials which are governed by separate legislation.
With regard to periodic reports, the US and the EU favour provision of an annual safety report as opposed to the six monthly line listing. In 2011, EU Detailed Guidance was updated which no longer requires ethics committees to receive line listings. HRECs, investigators and institutions are notified by the sponsor of any safety issues in an expedited fashion as and when they arise.

4.2. Annual Safety Reports (ASRs)

The purpose of an annual safety report is to provide regulatory authorities and ethics committees with an annual review and evaluation of safety information in order assure regulators and ethics committees that the sponsor is adequately monitoring the safety profile of the investigational product.

4.2.1. Australian Requirements

The Position Statement suggests HRECs should receive either an updated investigator’s brochure (IB) or the current, approved Product Information (PI) or an Annual Safety Report (ASR) or other reports consistent with the National Statement. The Position Statement accepts the EU format annual safety reports (ASRs) if these have already been produced for international distribution. For non-commercial trials, it states the following:

“...for trials that are investigator or collaborative group sponsored in which an IB, EU ASR or PI are not available, then a trial update may be submitted that provides appropriate review of safety information in the previous 12 months.”

4.2.2. International Requirements

Annual safety reports are provided to ethics committees in both the US and EU. In 2010, guidelines were developed by the ICH Expert Working Group to harmonise the format, content and scheduling of annual safety reports in ICH regions. The new format is known as a Development Safety Update Report (DSUR).

In New Zealand, a simpler format than the DSUR has been adopted. See Point 206 (p 45) of New Zealand’s Health and Disability Ethics Committee SOPs which provides information relating to the content and format of the annual report to New Zealand ethics committees.

4.3. Updated Investigator’s Brochure (IB) or Product Information (PI)

4.3.1. Australian Requirements

The Position Statement allows investigators to send an updated IB or current approved PI in place of an annual safety report but it also states that for some trials the IB or PI “may not be available”. The Position Statement therefore does not provide any clarity on how the ‘expectedness’ assessment for an adverse reaction would take place in the absence of an IB or PI.

4.3.2. International Requirements

European guidance emphasises that one of the key purposes of an IB or PI, is the role these documents play in the assessment of the ‘expectedness’ of an adverse reaction. In 2016, European law will require a specific section in the IB, called the Reference Safety Information (RSI)10, to contain the information required to assess the expectedness of all adverse reactions. The ICH E2F annual safety report guidance (followed by all ICH regions) has also adopted this term. In Europe, a single document containing the RSI

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10 A separate section allows the IB to be changed independently of the RSI
must be chosen for each trial and must be either the IB, the PI or another country’s equivalent of the PI, such as a European SmPC.

IBs must be reviewed at least annually. The IB or PI that was in place at the beginning of the annual safety reporting period is appended to the annual safety report (DSUR). If the IBs and PIs are changed significantly during the reporting period, (e.g. new contraindications, warnings, interactions) ethics committees and regulatory authorities are notified in the form of a substantial amendment. Investigators receive updated investigator’s brochures at least annually and if more frequent changes are made, they receive all new versions of the IB or PI whether the change meets the definition of a substantial amendment, or not.

5. Other Relevant Considerations

There are a number of other considerations with respect to safety reporting which are not addressed by the Position Statement, but which are, nonetheless, considered important to ensure an efficient safety reporting system in Australia. These are outlined below.

5.1. Standardisation of all Safety Reporting Terminology Used by Approval Bodies

An analysis of safety reporting guidelines and policies across Australia has highlighted a variety of terminology in use. For example, there are a number of terms used to define ‘SUSAR’ including; ‘Serious Unexpected Suspected Adverse Reaction’ (used in the National Statement), Suspected Unexpected Serious Adverse Reaction (used in the Position Statement and in the NMA Monitoring and Reporting Tables) and Serious and Unexpected Adverse Drug Reaction (used by the TGA). This lack of consistency may preclude efforts to ensure there is a common understanding of all requirements amongst stakeholders.

In order to determine whether a SUSAR has occurred, three assessments must be performed: Seriousness, Causality and Expectedness (see Appendix 2). In both US and EU legislation, a discrete ‘term’ is introduced to distinguish between the outcomes of each of these assessments so that those assessing events do not miss or undervalue any of these assessments.

5.2. Clarification of the Role and Function Data Safety & Monitoring Boards (DSMB)

5.2.1. Australia

During the approvals process, HRECs must satisfy themselves that each trial’s safety monitoring plans are robust and also commensurate to the risks, size and complexity of the trial. Data Safety and Monitoring Boards (DSMBs) are not required or appropriate for all trials, but if they are convened, HRECs generally have to confirm whether they are sufficiently independent and also what their role and function will be. Advice on DSMBs differs slightly between the National Statement and the Position Statement:

Section 3.3.20 of the National Statement defines the requirement for a DSMBs to be appointed based on whether the clinical trials is multi-centre or local:

“(c) for a large multi-centre trial, a Data and Safety Monitoring Board (DSMB) is used and there is a mechanism for informing the HREC of any relevant emerging data from the DSMB;
(d) for a local trial, there is an identified person/s or committee with suitable expertise to assist and advise the HREC about reports of serious adverse events."

By contrast, the Position Statement describes the DSMB as one of a range of mechanisms that may be appropriate, not only based on the whether a trial is large and multi-centre, but also based on its risks and complexity.
5.2.2. Internationally

The importance of a properly convened DSMB (known as a Data Monitoring Committee) is well accepted, with a number of international guidance documents explaining their role and function. The FDA’s guidance clearly describes when these committees are appropriate: (Section 2.1 and 2.2 of FDA Guidance: Establishment and Operation of Clinical Trial Data Monitoring Committees) and further useful guidance has been written by the European Medicines Agency.

Both the US and EU emphasise the importance of ensuring there is a systematic and transparent approach to the structure and operation of DSMBs and recommend that a charter is prepared for every DSMB before the start of the trial. As such, for those trials that require a DSMB, the 2016 European Clinical Trials Regulation, will require a copy of the trial’s DSMB Charter\(^{11}\) as part of the application for approval.

5.3. Safety Reporting Pathways for Trials Approved Under Single Ethical Review Mechanisms

With respect to reporting pathways for clinical trials approved under single ethical review, the UK system for safety reporting is the most comparable, as single ethical review and approval for multi-centre trials has been in place in the UK since 2004. Many of the issues inherent in the Australian system have already been addressed in the UK and have resulted in significant time and resource savings for both investigator and sponsor. In the UK:

1. Sponsors generally send safety reports (SUSARs) directly to the MHRA and the ethics committee and forward to all investigators in parallel;
   All ‘confirmation of receipt’ letters from ethics committees are filed by the entity or individual responsible for sending the report (with the sponsor/CPI copied in). They are not routinely processed back through local Principal Investigators and their institutions\(^{12}\).
2. Principal Investigators are not required to comment on all safety reports, negating the requirement for events to be processed through all Principal Investigators.

6. Safety Reporting: Medical Device Trials

In order to fully assess a uniform approach to safety monitoring and reporting there is also a need to consider current practices in reporting on clinical trials that involve the use of medical devices.

The TGA requires all clinical trials involving medical devices to be run to ISO 14155 Clinical investigation of medical devices for human subjects –Good clinical practice, which is internationally recognised and cited by both the FDA and EU in guidance documents. An updated version of ISO 14155:2011 has replaced the 2003 version and has closely harmonised the good clinical practice requirements for device trials with those for investigational products (ICH GCP). This describes the sponsor’s responsibilities for safety reporting and confirms the sponsor is responsible for the ongoing safety evaluation of the clinical investigation.

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\(^{11}\) A proposed charter has been developed by the DAMOCLES study group - *The Lancet* 365:711-722, 2005

\(^{12}\) When considering this approach within Australia from a GCP perspective, it is worth noting that European GCP inspectors recognise that ICH GCP was written when *each* investigator’s HREC approved the trial. As this is no longer the case, inspectors accept that the documentation in the local PI’s site file may not be the same as the documentation retained by the CPI.
With regard to safety reporting, there is a direct parallel between the definitions for investigational products and devices. However, the following additional definitions in ISO 14155:2011 are provided to address the different failure modes of medical devices:

- **Adverse Device Effect** - insufficient or inadequate instructions for use, deployment, implantation, installation, or operation, or any malfunction of the investigational medical device
- **Device Deficiencies** - inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety or performance
- **Adverse events** are not restricted to participants; can also be ‘users or other persons’

The Australian Regulatory Guidelines for Medical Devices (ARGMD) published by TGA is the most comprehensive document outlining reporting requirements for medical device trials under the CTN and CTX schemes (see p 274). This document requires Unanticipated Serious Adverse Device Effects (USADEs) to be reported to the TGA within the same timeframes as SUSARs. Safety reporting to ethics committees should be, ‘as required by the HREC’.

The TGA also expects that a system is in place to track the recipient of the device for the lifetime of the device.

The National Statement Section 3.3.3 (d) requires “research meets the relevant requirements of the CPMP/ICH Note for Guidance on Good Clinical Practice (CPMP/ICH-135/95), ISO 14155: Clinical Investigation of Medical Devices, and the TGA”.

The Position Statement does not provide any guidance for trials involving medical devices. In the event that the Position Statement is amended, it would be prudent to also include references to safety reporting with respect to medical devices and for these to follow a similar system to that used for investigational products.
### APPENDIX 1: Comparison Tables

#### SPONSOR REPORTING TO REGULATORY AUTHORITIES

<table>
<thead>
<tr>
<th>US</th>
<th>EU</th>
<th>EU FROM 2016</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. SUSARs must be sent to the FDA (within seven days for fatal and life threatening SUSARs and fifteen days for all other SUSARs)</td>
<td>1. SUSARs (within seven days for fatal and life threatening SUSARs and fifteen days for all other SUSARs)</td>
<td>1. SUSARs (within seven days for fatal and life threatening SUSARs and fifteen days for all other SUSARs)</td>
</tr>
<tr>
<td>2. Any such findings that would result in safety-related change in the protocol, informed consent, investigator’s brochure such as:</td>
<td>2. Any safety issues which might materially alter the current benefit-risk assessment of an investigational product (IP)</td>
<td>2. Unexpected events which affect the benefit-risk balance of a clinical trial (within fifteen days)</td>
</tr>
<tr>
<td>- Findings from other studies</td>
<td>3. Urgent safety measures within three days</td>
<td>3. Urgent safety measures within seven days</td>
</tr>
<tr>
<td>- Findings from animal or in vitro testing</td>
<td>4. Temporary halt/early termination within fifteen days</td>
<td>4. Temporary halt/early termination within fifteen days</td>
</tr>
<tr>
<td>- Increased rate of occurrence of serious suspected adverse reactions</td>
<td>Annual Safety Reports: The E2F Developmental Safety Update Report format has been adopted</td>
<td>Annual Safety Reports: The E2F Developmental Safety Update Report format has been adopted</td>
</tr>
</tbody>
</table>

#### AUSTRALIA (THE CURRENT POSITION STATEMENT)

1. SUSARs (occurring in Australia only) must be sent to the TGA within seven days for fatal and life threatening SUSARs and fifteen days for all other SUSARs.
2. Any significant safety issue (SSI) within 72 hours.
   N.B. The TGA’s Australian Clinical Trials Handbook also requires sponsors to report to HRECs both urgent safety measures and premature termination of a trial.

**Comment:** For trials run under the CTN Scheme, the TGA does not request overseas SUSARs or annual safety reports as the Therapeutic Goods Regulation delegates the responsibility for monitoring the progress and conduct of the trial to the HREC.

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13 In 2010, guidelines were developed by the ICH Expert Working Group to harmonise the format, content and scheduling of annual safety reports which are required by Regulators in ICH regions.
## SPONSOR REPORTING TO INVESTIGATORS

<table>
<thead>
<tr>
<th>US</th>
<th>EU</th>
<th>EU 2016</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. SUSARs (within seven days for fatal and life threatening SUSARs and fifteen days for all other SUSARs)</td>
<td>1. A line listing (blinded) of SUSARs in periods as warranted by the nature of the research project/clinical development project and the volume of SUSARs generated. This line listing should be accompanied by a concise summary of the evolving safety profile of the investigational product (IP)</td>
<td>No detail</td>
</tr>
<tr>
<td>2. Any such findings that would result in safety-related change in the protocol, informed consent, investigator’s brochure such as: • Findings from other studies • Findings from animal or in vitro testing • Increased rate of occurrence of serious suspected adverse reactions</td>
<td>2. Any safety issues which might materially alter the current benefit-risk assessment of an IP</td>
<td></td>
</tr>
</tbody>
</table>

## AUSTRALIA (THE CURRENT POSITION STATEMENT)

Sponsors should keep investigators up to date with safety issues and provide investigators with periodic information “to facilitate investigator submission to the relevant HREC(s)”:  

1. **In a prompt manner** – Information which could adversely affect the safety of subjects, materially impact the continued ethical acceptability of the trial or that requires (or indicates the need for) a change to the trial protocol, including changed safety monitoring.  
2. **At least six monthly** – A line listing.  
3. **At least annually** – An updated Investigator Brochure’s (IB), or an EU Annual Safety Report (ASR), or similar format report, or current, approved Product Information (PI), if appropriate (e.g. in a study for a product approved in Australia or where an IB is no longer maintained). Other reports consistent with Section 5.5.5 of the National Statement and Good Clinical Practice (GCP) as adopted by the TGA. 
   For trials that are investigator or collaborative group sponsored in which an IB, EU ASR or PI are not available, then a trial update may be submitted that provides appropriate review of safety information in the previous twelve months.  
   • Sponsors should establish safety monitoring processes that are commensurate with the risk, size and complexity of the proposed research.  
   • Sponsors need to include clear advice as to whether the information requires or indicates the need for a change in the trial protocol including changed safety monitoring.  
   • SUSARs are NOT routinely required to be sent to investigators.  

**Comment:** The EU system is less burdensome for investigators as reports specifically produced for ethics committees (e.g. annual safety reports) do not have to be processed through investigators. The legislation allows sponsors to report directly to the relevant ethics committee.
Investigators to report promptly to the IRB all ‘unanticipated problems’ involving risk to human subjects or others. Guidance on safety reporting to IRBs\(^\text{14}\) suggested that adverse events should be considered unanticipated problems:

“only if it were unexpected, serious, and would have implications for the conduct of the study”

The guidance also states that for multicentre trials, the sponsor is in a better position to process and analyse adverse event information for the entire study so the investigator may rely on the sponsor’s assessment and provide a report prepared by the sponsor or the sponsor may report directly to the IRB if the IRB has made an explicit agreement for this to happen.

Annual Safety Reports: E2F Developmental Safety Update Report

| SPONSOR/INVESTIGATOR REPORTING TO ETHICS COMMITTEES |
|-----------------|-----------------|
| **US** | **EU** |
| Investigators to report promptly to the IRB all ‘unanticipated problems’ involving risk to human subjects or others. Guidance on safety reporting to IRBs\(^\text{14}\) suggested that adverse events should be considered unanticipated problems: “only if it were unexpected, serious, and would have implications for the conduct of the study” | Sponsors to report directly to the ethics committee, all SUSARs occurring in the clinical trial concerned, if the SUSARs occurred in the territory of that Member State (within seven days for fatal and life threatening SUSARs and fifteen days for all other SUSARs) |
| The guidance also states that for multicentre trials, the sponsor is in a better position to process and analyse adverse event information for the entire study so the investigator may rely on the sponsor’s assessment and provide a report prepared by the sponsor or the sponsor may report directly to the IRB if the IRB has made an explicit agreement for this to happen. | The Regulation leaves it to the discretions of Member States to make provision for Ethics Committee involvement in clinical trial safety reporting. It is not mandated. Member States will be free to choose the extent and nature of safety reporting to ethics committees |

**AUSTRALIA (THE CURRENT POSITION STATEMENT)**

1. To institution (or HREC as specified by institution) AEs or SAEs occurring at their site(s).

To HREC responsible for the trial:

2. **In a prompt manner** – Information which could adversely affect the safety of subjects, materially impact the continued ethical acceptability of the trial or that requires (or indicates the need for) a change to the trial protocol, including changed safety monitoring.

3. **At least six monthly** – A line listing.

4. **At least annually** – An updated Investigator Brochure’s (IB), or an EU Annual Safety Report (ASR), or similar format report, or current, approved Product Information (PI), if appropriate (e.g. in a study for a product approved in Australia or where an IB is no longer maintained).

Other reports consistent with Section 5.5.5 of the National Statement and Good Clinical Practice (GCP) as adopted by the TGA.

For trials that are investigator or collaborative group sponsored in which an IB, EU ASR or PI are not available, then a trial update may be submitted that provides appropriate review of safety information in the previous twelve months.

**Comment**: The US and EU systems are less burdensome for HRECs as they are not required to process AEs and SAEs or six monthly line listings. (SUSARs are sent to HRECs in the US and EU at present, but the EU will not mandate this from 2016).

\(^{14}\) In 2009, the FDA produced guidance on [Adverse Event Reporting to IRBs](http://www.fda.gov/AboutFDA/CentersOffices/OD/hana/ucm098337.htm)
APPENDIX 2: Safety Reporting Definitions Flowchart: Investigational Product Trials

15 Adapted from material produced by T Symons Associates Ltd for the NIHR Clinical Trials Toolkit
<table>
<thead>
<tr>
<th>DEFINITIONS</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Investigational Product (IP)</strong></td>
<td>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, or when used to gain further information about an approved use.</td>
</tr>
<tr>
<td><strong>Adverse Event (AE)</strong></td>
<td>Any untoward medical occurrence in a patient or clinical trial participant administered a medicinal product and which does not necessarily have a causal relationship with this treatment.</td>
</tr>
</tbody>
</table>
| **Adverse Reaction (AR)**                                                 | Any untoward and unintended response to an investigational product related to any dose administered.  
| **Comment:** All adverse events judged by either the reporting investigator or the sponsor as having a *reasonable causal relationship* to an investigational 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.  
| **Comment:** 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. |
| **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.  
| **Comment:** 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.  
| *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 which hypothetically might have caused death if it were more severe. |
| **Unexpected Adverse Reaction (UAR)**                                     | An adverse reaction, the nature or severity of which is not consistent with the reference safety information (RSI).  
<p>| <strong>Comment:</strong> The RSI should be contained in the investigator's brochure for an unapproved investigational product or product information for an approved investigational product (or another country’s equivalent of the product information) |
| <strong>Suspected Unexpected Serious Adverse Reactions (SUSAR)</strong>                | An adverse reaction that is both serious and unexpected. |</p>
<table>
<thead>
<tr>
<th>Term</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Investigator’s Brochure (IB)</td>
<td>The document containing a summary of the clinical and non-clinical data relating to an investigational product which are relevant to the study of the product in humans</td>
</tr>
<tr>
<td>Product Information (PI)</td>
<td>A product information (PI) provides a summary of the scientific information relevant to the safe and effective use of a prescription medicine</td>
</tr>
<tr>
<td>Reference Safety Information (RSI)</td>
<td>The information contained in either an investigator’s brochure or a product information (or another country’s equivalent of a product information) that contains the information used to determine what adverse reactions are to be considered as expected adverse reactions and on the frequency and nature of those adverse reactions</td>
</tr>
<tr>
<td>Safety Critical Adverse Events</td>
<td>Adverse events and/or laboratory abnormalities identified in the protocol as critical to safety evaluation that should be reported to the sponsor according to the reporting requirements specified in the protocol</td>
</tr>
<tr>
<td>Significant Safety Issue (SSI)</td>
<td>A safety issue which could adversely affect the safety of participants, materially impact on the continued ethical acceptability of the trial or require a change to the trial protocol, including changed safety monitoring</td>
</tr>
<tr>
<td>Urgent Safety Measure (USM)</td>
<td>A measure required to be taken in order to protect a trial participant against any immediate hazard to their health or safety</td>
</tr>
</tbody>
</table>
| Reportable Protocol Violation (RPV) | A breach likely to affect to a significant degree:  
  a) The safety or physical or mental integrity of the trial participant  
  b) The scientific value of the trial |
APPENDIX 3: Safety Reporting Definitions Flowchart: Medical Device Trials\textsuperscript{16}

\begin{figure}
\centering
\includegraphics[width=\textwidth]{flowchart.png}
\end{figure}

\textsuperscript{16} Adapted from material produced by T Symons Associates Ltd for the \textit{NIHR Clinical Trials Toolkit}
## DEFINITIONS

<table>
<thead>
<tr>
<th>Term</th>
<th>Definition</th>
</tr>
</thead>
</table>
| **Medical Device** | Any instrument, apparatus, implement, machine, appliance, implant, software, material or other similar or related article  
 a) intended, by the person under whose name it is or is to be supplied, to be used for human beings for the purpose of one or more of the following:  
 1. diagnosis, prevention, monitoring, treatment or alleviation of disease;  
 2. diagnosis, monitoring, treatment, alleviation of or compensation for an injury or handicap;  
 3. investigation, replacement or modification of the anatomy or of a physiological process;  
 4. supporting or sustaining life;  
 5. control of conception;  
 6. disinfection of medical devices, and  
 b) which does not achieve its primary intended action in or on the human body by pharmacological, immunological or metabolic means, but which may be assisted in its intended function by such means |
| **Adverse Event (AE)** | 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  
 **Notes:** 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 restricted to events related to investigational medical devices |
| **Adverse Device Effect (ADE)** | Adverse event related to the use of an investigational medical device  
 **Notes:** 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 |
| **Investigator’s Brochure (IB)** | Compilation of the current clinical and non-clinical information on the investigational medical device(s) relevant to the clinical investigation. |
| **Serious Adverse Event (SAE)** | Adverse event that:  
 a) led to death,  
 b) led to serious deterioration in the health of the participant, that either resulted in:  
 1. a life-threatening illness or injury, or  
 2. a permanent impairment of a body structure or a body function, or  
 3. in-patient or prolonged hospitalization, or  
 4. medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function,  
 c) led to foetal distress, foetal death or a congenital abnormality or birth defect  
 **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. |
| **Serious Adverse Device Effect (SADE)** | An adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event |
| **Unanticipated Serious Adverse Device Effect (USADE)** | 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  
 **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 |
| **Device Deficiencies** | Inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety or performance. Device deficiencies include malfunctions, use errors, and inadequate labelling |
| **Significant Safety Issue (SSI)** | A safety issue which could adversely affect the safety of participants, materially impact on the continue ethical acceptability of the trial or require a change to the trial protocol, including changed safety monitoring. |
| **Urgent Safety Measure (USM)** | A measure required to be taken in order to protect a trial participant against any immediate hazard to their health or safety |
| **Reportable Protocol Violation (RPV)** | A breach likely to affect to a significant degree:  
 a) The safety or physical or mental integrity of the trial participant  
 b) The scientific value of the trial |
### APPENDIX 4: OVERVIEW OF CURRENT v INTERNATIONAL PRACTICE

#### Monitoring Tables for NSW, QLD, VIC, SA, ACT and WA (Jan 14)

<table>
<thead>
<tr>
<th>Single Case SAEs: No material impact on the trial (as assessed by PI)</th>
<th>International Practice</th>
</tr>
</thead>
<tbody>
<tr>
<td>All SAEs (under the responsibility of the HREC) are sent to HRECs by the PI/CPI (except VIC which requires as per Position Statement)</td>
<td>In the US and EU, investigators and HRECs are not expected to make judgements on the impact of the trial based on single case events or partial datasets of SAEs.</td>
</tr>
<tr>
<td><strong>Timeline:</strong> Expedited</td>
<td>No SAEs (or SUSARs) are sent directly to HRECs and institution by investigators. Instead, only SAEs that are both related to the investigational product and unexpected (i.e. SUSARs) are expedited to HRECs by the following route:</td>
</tr>
<tr>
<td><strong>Other parties copied in:</strong> PI/CPI/RGO (varies across States and Territories).</td>
<td>- All SAEs reported to the sponsor by the investigator (within 24 hrs)</td>
</tr>
<tr>
<td><strong>HREC Action:</strong> HRECs are generally required to review and respond back through CPI.</td>
<td>- The sponsor confirms whether the SAE meets the definition of a SUSAR* and once confirmed, expedite to all parties required by regional law, within the 7/15 day timeframe</td>
</tr>
<tr>
<td><strong>RGO Action:</strong> RGOs are generally required to respond back through PI.</td>
<td>*In the US, the sponsor is not obliged to report to regulator/investigator/HREC if, in their opinion the investigator’s assessment of causality or expectedness is incorrect and therefore the event does not meet the definition of a SUSAR. In the EU, if the sponsor believes the investigator’s assessment is incorrect, they must report to the regulator/HREC, but can also report their opinion as well, i.e. The investigator’s assessment cannot be downgraded.</td>
</tr>
</tbody>
</table>

#### Single Case SAEs: Material impact on the trial (as assessed by PI)

<table>
<thead>
<tr>
<th>All SAEs (under the responsibility of the HREC) are sent to HRECs by the PI/CPI</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Timeline:</strong> Expedited</td>
<td></td>
</tr>
<tr>
<td><strong>Other parties copied in:</strong> PI/CPI/RGO (varies across States and Territories).</td>
<td></td>
</tr>
<tr>
<td><strong>HREC Action:</strong> HRECs are generally required to review/respond back through the CPI.</td>
<td></td>
</tr>
<tr>
<td><strong>RGO Action:</strong> RGOs are generally required to respond back through the PI.</td>
<td></td>
</tr>
</tbody>
</table>

### Australian and International SUSARs Industry Report or DSMB Report

#### Periodic reports are required to be sent to HRECs by PI/CPI:

<table>
<thead>
<tr>
<th>Timeline: Six monthly intervals (except ACT which only requires an annual report).</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Other parties copied in:</strong> CPI/PI (and the RGO in WA and ACT).</td>
<td></td>
</tr>
<tr>
<td><strong>HREC Action:</strong> Acknowledgment/decision letter is sent to CPI (except in SA where it is only sent if further action is necessary).</td>
<td></td>
</tr>
<tr>
<td><strong>RGO Action:</strong> In ACT and WA acknowledgement/decision letter is sent.</td>
<td></td>
</tr>
</tbody>
</table>

### International SUSARs Industry Report or DSMB Report

In the US and EU, six monthly reports are not required but instead:

- **Annual safety reports are sent to HRECs for both commercial and non-commercial trials. The current investigator’s brochure (IB) or product information (PI) is appended to this report.**
- **If the IB or PI is updated with important new information during the reporting period, the sponsor will send the new version to the HREC as a substantial amendment. All IB/PI updates are sent to investigators who forward to their institution if a substantial amendment.**
- **Significant findings arising from a DSMB (or alternative safety committee) that impact on the trial, are reported as and when they arise. These may be reported as significant safety issues (usually through the substantial amendment route) or as a temporary or permanent halt of a trial.**
- **Reporting Pathway:** Sponsor directly to HREC and investigators.
### Significant Safety Issues (SSIs)

There is no overarching definition other than the requirement for the PI to judge whether each SAE has "material impact on the conduct of a study".

### Significant Safety Issues (SSIs)

Significant safety issues are defined more clearly in both the US and the EU (Section 3.5.1.)
- **Reporting Pathway**: Sponsor directly to HREC and investigators. Investigators report on to their institution.
- **Timeline**: 3-15 days

### Urgent Safety Measures (USMs)

Some states indicate that the CPI is responsible for ‘urgent safety related modifications’. It is not clear from the tables whether the action can be implemented before HREC approval, to protect a participant from an immediate hazard.

- **Timeline**: Within 5 working days.

### Urgent Safety Measures (USMs)

In the EU, this type of measure can be instigated by either the investigator or sponsor and can be implemented before seeking approval from HRECs or institutions in order to protect the participant from an immediate hazard. They are reported, post hoc as a substantial amendment.
- **Reporting Pathway**: Investigator to sponsor and local institution. Then sponsor to HREC and all other investigators. If instigated by sponsor, then directly to HREC and investigators (who would forward to their institution).
- **Timeline**: Currently within 3 days but from 2016, within 7 days

### Protocol Deviations and Protocol Violations

Both protocol deviations and protocol violations are required to be reported by the CPI/PI to HRECs in all States and Territories.

- **HREC Action**: Acknowledgment letter sent to CPI/PI.
- **RGO Action**: No action listed in Tables.
- **Timeline**: Not specified.

### Protocol Deviations and Protocol Violations

**Protocol Deviations**: There is no internationally recognised definition, but protocol deviations can be defined as, “non-compliances with the approved study protocol which do not have any impact on the safety of participants, the conduct of the trial or the integrity of trial data”. They are not required to be reported to HRECs or institutions. Sponsors will collate all deviations (and violations) as part of their monitoring processes and for ongoing trial management.

**Reportable Protocol Violations (known as Serious Breaches in the EU)**: Protocol violations that meet the definition of a ‘serious breach’ are considered as reportable:

A Serious Breach of Good Clinical Practice (GCP) or the protocol:

“A breach likely to affect to a significant degree:
   a) The safety or physical or mental integrity of the trial participant
   b) The scientific value of the trial”

Serious breaches are reported to the sponsor by the investigator (or detected by the sponsor during monitoring). Sponsors then report to HRECs. Investigators are required to notify their institutions. **Timeline: 7 days**
APPENDIX 5: Summary of the Responsibilities for Safety Reporting According to the National Statement (NS) and Position Statement (PS)

**HREC**

- SAEs (NS)
- AEs and SAEs (PS)
- “Any new safety information from other published or unpublished studies that may have an impact on the continued ethical acceptability of the trial or may indicate the need for amendments to the trial protocol” (NS)
- “Information which materially impacts the continued ethical acceptability of the trial” (PS)
- “Information that requires, or indicates the need for, a change to the trial protocol, including changed safety monitoring in the view of the investigator or sponsor”. (PS)
- SUSARs—at least six monthly: Listings of all SUSARs, Australian and International, including sponsor and investigator comments as to whether action is planned for the trial (PS)
- “An updated Investigator Brochure, or an EU ASR (or similar format report), or current, approved Product Information (PI), if appropriate (e.g. in a study for a product approved in Australia or where an Investigator Brochure is no longer maintained) and other reports consistent with section 5.5.5 of the National Statement and Good Clinical Practice (GCP) as adopted by the Therapeutic Goods Administration (TGA)”. (PS)

**TGA**

- Individual case safety reports in accordance with CPMP/ICH/377/95

**SPONSOR**

- Keep investigator up to date with safety issues in the trial
- Provide investigators with periodic information to facilitate investigator submission to the relevant HREC (PS)

**INVESTIGATOR** (CPI or PI)

- All AEs and SAEs occurring at their site in accordance with the study protocol.
- SAEs within 24 hours (PS)

- AEs and SAEs “in accordance with individual institutional requirements” (PS)

**INSTITUTION**

**KEY:**
- AE - Adverse Event
- SAE - Serious Adverse Event
- CPI - Coordinating Principal Investigator
- HREC - Human Research Ethics Committee
- IB - Investigator’s Brochure
- PI - Product Information
- PI - Principal Investigator
- SOP - Standard Operating Procedure
N.B. Similar reporting pathways would apply to medical devices trials.

**APPENDIX 6: Option for Simplifying Existing Safety Reporting Arrangements**

- **HREC**
  - Significant Safety Issues
  - Urgent Safety Measures
  - Premature Termination/Temporary Halt
  - Reportable Protocol Violations
  - Annual Safety Report
  - IB/PI Updates (if substantial amendments)

- **INSTITUTION**
  - Significant Safety Issues
  - Urgent Safety Measures
  - Premature Termination/Temporary Halt
  - Local SUSARs (for information purposes)
  - Local Reportable Protocol Violations
  - IB/PI Updates (if substantial amendment)

- **SPONSOR**
  - Significant Safety Issues
  - Urgent Safety Measures
  - Premature Termination/Temporary Halt
  - SUSAR (if required by sponsor’s SOPs)
  - IB/PI Updates
  - Safety Critical AEs, SAEs, SUSARs (as per protocol)
  - Reportable Protocol Violations
  - Urgent Safety Measures

- **INVESTIGATOR (CPI** or PI)
  - Significant Safety Issues
  - Urgent Safety Measures
  - Premature Termination/Temp. Halt
  - SUSAR (if required by sponsor’s SOPs)
  - IB/PI Updates

**KEY:**
- AE - Adverse Event
- SAE - Serious Adverse Event
- CPI - Coordinating Principal Investigator
- HREC - Human Research Ethics Committee
- TGA - Therapeutics Goods Administration
- SPONSOR - Sponsor
- INVESTIGATOR - Investigator
- INSTITUTION - Institution
- HREC - Human Research Ethics Committee
- TGA - Therapeutics Goods Administration
- SPONSOR - Sponsor
- INVESTIGATOR - Investigator
- INSTITUTION - Institution
- HREC - Human Research Ethics Committee
- TGA - Therapeutics Goods Administration

*For investigator-led trials, the CPI may take on the sponsor’s responsibility for the notification of safety information to the TGA, HREC and investigator.

** The CPI is copied in to all correspondence sent to the PI and HREC.

N.B. Similar reporting pathways would apply to medical devices trials.