Response to the consultation on updating arrangements for safety monitoring and reporting of clinical trials in Australia
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APPENDIX 1: Possible option for Simplifying Existing Safety Reporting for Investigational Product Trials .... 21
1. List of Acronyms

AE    Adverse Event
ADE   Adverse Device Effect
AHEC  Australian Health Ethics Committee
ARCS  (Previously the) Association of Regulatory and Clinical Scientists
ASR   Annual Safety Report
AR    Adverse Reaction
CPI   Coordinating Principal Investigator
CRO   Contract Research Organisation
CTN   Clinical Trial Notification
DIL   Dear Investigator Letter
DMC   Data Monitoring Committee
DSMB  Data Safety & Monitoring Board
EU    European Union
FDA   Food and Drugs Administration
GCP   Good Clinical Practice
HREC  Human Research Ethics Committee
IB    Investigator’s Brochure
ICH   International Conference on Harmonisation
IP    Investigational Product
IRB/IEC Independent Review Board/Independent Ethics Committee
ISO   International Organisation of Standardisation
MHRA  Medicines and Healthcare Product Regulatory Agency
NHMRC National Health and Medical Research Council
NMA   National Mutual Acceptance
NZ    New Zealand
PI    Principal Investigator
PI    Product Information
SADE  Serious Adverse Device Effect
SAE   Serious Adverse Event
SAR   Serious Adverse Reaction
SmPC  Summary of Product Characteristics
SOP   Standard Operating Procedure
SSI   Significant Safety Issue
SUSAR Suspected Unexpected Serious Adverse Reaction
TGA   Therapeutic Goods Administration
UK    United Kingdom
US    United States
USADE Unanticipated Serious Adverse Device Effect
USM   Urgent Safety Measure
2. Executive Summary

In December 2014, T Symons Associates Pty Ltd was engaged by the NHMRC to conduct a targeted national consultation to seek stakeholders’ views on current Australian practices for safety monitoring and reporting, including whether a new framework was required. The aim of this report is to present the findings from the consultation and to set out the possible options for a revised system. The key findings are summarised in Table 1.

<table>
<thead>
<tr>
<th>Key Findings - Stakeholder Feedback</th>
<th>Options for Further Work</th>
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<tbody>
<tr>
<td>The safety reporting and monitoring framework in Australia should be <strong>aligned with international practice</strong> to promote harmonisation. The current system creates barriers to conducting multicentre and multinational trials. Feedback derived from Questions 1, 2, 3, 5, 6, 8, 9, 11, 13 and 14</td>
<td>Develop a revised framework for safety monitoring and reporting in clinical trials that is aligned with international practice and Australian regulatory requirements. Ensure that any new framework incorporates a risk-adapted approach to safety monitoring.</td>
</tr>
<tr>
<td><strong>Roles and responsibilities are often inappropriate</strong> and should be aligned with international practice. The duplication of activity and double handling of safety reports should be addressed.</td>
<td>Ensure the specific responsibilities of the investigator, institution, HREC and sponsor are aligned with international practice including ICH GCP, ISO14155 and the 2016 EU Clinical Trial Regulation. Consider placing particular emphasis on the following actions:</td>
</tr>
<tr>
<td>The responsibility for the review of <strong>single case events</strong> for ongoing safety monitoring should lie with the trial sponsor as they are best placed to aggregate/analyse these reports. It should be the outcome of the review that is sent to HRECs and institutions. Some flexibility in reporting to HRECs may be appropriate for a subset of trials. Incorrect emphasis is placed on the investigator’s review of single case events as an appropriate means of drawing conclusions as to the continued ethical acceptability of a trial. Guidance to clarify and explain all revised requirements, responsibilities and processes would be required. Feedback derived from Questions 1, 2, 4, 5 and 13</td>
<td>• Ensure that any new framework places the responsibility for the ongoing safety analysis of a trial with the sponsor. • Remove the requirement for investigators to make immediate judgements on the continued ethical acceptability of a trial based on single case events. • Review and rationalise the reporting of single case events/protocol deviations to HRECs and institutions to ensure these bodies only receive reports that impact on their roles. • Ensure documentation and guidance supports these changes.</td>
</tr>
<tr>
<td><strong>Inappropriate Reporting Pathway</strong> The current safety reporting pathway places a considerable burden on the coordinating principal investigator. It should be amended to reflect the adoption of the single ethical review system. Feedback derived from Questions 1, 2, 3, and 13</td>
<td>Amend the reporting pathway to place the sponsor at the centre of the communication cascade in line with European practice, thereby allowing sponsors to report directly to HRECs/ investigators in parallel).</td>
</tr>
<tr>
<td>The <strong>lack of standardisation/consistency in safety reporting practices across Australia places an unnecessary burden on both investigators and sponsors. The lack of clarity of roles and responsibilities</strong> should be addressed, as current requirements are ambiguous and the purpose of many of the reporting requirements is questioned. Feedback derived from Questions 1, 2, 3, 5, 6, 8, 9, 11,</td>
<td>Develop standard reporting procedures and ensure that all revised requirements are communicated in relevant guidance so that the added value of each process or activity is recognised by all parties.</td>
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### Sponsor Capabilities

Sponsors that do not have access to pharmacovigilance department support (e.g. sponsors of small biotech or investigator-led trials) would benefit from additional support and guidance to help ensure they meet all regulatory requirements.

Feedback derived from Questions 2, 4, 6, 10, 12 and 14

### Reassurance for HRECs

HRECs require reassurance that sponsors are adequately monitoring the safety of participants as the trial progresses.

Feedback derived from Questions 1, 7 and 8

### The safety reporting terminology should be standardised

Guidance should be produced to clarify all terminology associated with safety reporting and monitoring as described in the consultation paper.

Any guidance produced should reference standard terminology to promote a common understanding of all requirements.

Feedback derived from Questions 5, 6, 10, 11 and 14

### Proposed Simplified Reporting Arrangements

The proposed simplified reporting arrangements (now in Appendix 1) represent a reasonable approach for a new safety and monitoring reporting system in Australia.

Any revised system would require clear endorsement from both the TGA and the NHMRC.

Feedback derived from Questions 1, 2 and 13

<table>
<thead>
<tr>
<th>Sponsor Capabilities</th>
<th>Develop documentation and guidance for trial sponsors including:</th>
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<tr>
<td></td>
<td>• Guidance on DSMBs (or alternatives) to assist sponsors to develop appropriate, risk-based safety monitoring plans.</td>
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<tr>
<td></td>
<td>• Guidance on the risk assessment process to help sponsors identify and mitigate all trial-related risks and to allow approval bodies to quickly assess the adequacy of the sponsor’s plans.</td>
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</table>

| Reassurance for HRECs | Enable HRECs to receive reports from sponsors (particularly as part of an annual safety report) that allow them to confirm that the sponsor is monitoring the trial’s risk/benefit ratio in accordance with the safety monitoring plans and that those plans remain adequate. |

| The safety reporting terminology should be standardised | Consider a further consultation to standardise all safety reporting terminology/definitions. |

| Proposed Simplified Reporting Arrangements | Develop a simplified safety reporting framework for investigational product trials. |
|                                          | Develop a similar framework for medical devices trials taking into account device-specific adverse events and device deficiencies. Terminology should be sourced from ISO 14155. |

### 3. Consultation Scope and Methodology

The consultation was conducted through a mix of face to face meetings, presentations, teleconferences and an ARCS Interest Area Committee (IAC) webinar and online survey. There was productive engagement and input from all targeted stakeholder groups which included representatives from:

- The Therapeutic Goods Administration
- The pharmaceutical and medical device industry, including industry peak bodies
- State and Territory government departments
- Clinical trial networks (including cooperative groups and academic groups)

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1 Adapted from Appendix 6 of the ‘Consultation paper on updating clinical trial safety monitoring and reporting in Australia’ outlined the possible components for a new framework for Australian safety monitoring and reporting.
- Public and private hospital HRECs and research offices
- Clinical trial researchers and project coordinators

**Dissemination through peak bodies**
The consultation paper was disseminated through Medicines Australia, the Medical Technology Association of Australia (MTAA) and the Australian Private Hospitals Association (APHA). A sample of industry representatives, including pharmaceutical companies, devices companies and contract research organisations (CROs) were also contacted directly. Some of these representatives were also able to seek feedback from their Global Head Offices.

**Dissemination through government jurisdictions (States and Territories)**
Each jurisdiction was asked to provide the names of six key stakeholders, institutions and HRECs that were active in the area of clinical trials and therefore familiar with the current system.

In total, 30 responses were received: 28 written responses and 2 verbal responses (telephone feedback). The consultation was also made available on the NHMRC web site.

<table>
<thead>
<tr>
<th>Stakeholder Group</th>
<th>Responses</th>
<th>Stakeholder Representation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Industry</td>
<td>8</td>
<td>9 (Pharmaceutical/Medical Devices/CRO including Clinical Research Managers, Clinical Operations and Pharmacovigilance Staff, Clinical Research Associates)</td>
</tr>
<tr>
<td>ARCS Industry Webinar and Survey</td>
<td>2</td>
<td>50+ attendees (Pharmaceutical/CRO responding to a sub-set of industry-specific questions)</td>
</tr>
<tr>
<td>HRECs and Institutions</td>
<td>11</td>
<td>Public and private institutions</td>
</tr>
<tr>
<td>State/Territory Coordinated</td>
<td>4</td>
<td>HRECs, Institutional Governance Staff, Researchers and Site Staff within the States and Territories</td>
</tr>
<tr>
<td>Clinical Trials Centres</td>
<td>1</td>
<td>University</td>
</tr>
<tr>
<td>Peak Industry Bodies</td>
<td>1</td>
<td>Medical Technology Association of Australia representing the medical devices industry</td>
</tr>
<tr>
<td>Councils</td>
<td>1</td>
<td>Cancer Council Victoria representing 650 clinicians</td>
</tr>
<tr>
<td>Australian Clinical Trials Alliance (ACTA)</td>
<td>1</td>
<td>Representing 60 Clinical Trial Networks and over 10,000 clinicians</td>
</tr>
<tr>
<td>Therapeutic Goods Administration (TGA)</td>
<td>1</td>
<td>Regulatory Authority</td>
</tr>
</tbody>
</table>

The consultation sought views on a range of topics related to safety monitoring and reporting of clinical trials. Stakeholders were asked to respond to fifteen questions and a thematic analysis of the responses received was performed. The majority of stakeholders provided feedback on all questions; however, approximately one third of submissions comprised partial responses, either providing an overview of the issues associated with the current system or specific comments relating to a subset of questions.

**Conventions for descriptive terms used in this report**
The following words or phrases have been used throughout this report to indicate the level of agreement to the questions posed in the consultation.

<table>
<thead>
<tr>
<th>Term</th>
<th>Description</th>
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<tbody>
<tr>
<td>Unanimous</td>
<td>All stakeholders who provided specific feedback indicated agreement</td>
</tr>
<tr>
<td>Very Strong</td>
<td>Over 90% of respondent who provided specific feedback</td>
</tr>
</tbody>
</table>
4. Response to the Consultation Questions

The key themes that emerged from each question are discussed in more detail below and some of the ancillary topics arising from these themes are also outlined. Where there was a clear consensus that stakeholders supported a change or an action that endorsed a new framework, proposed options for a new framework are presented. Where further consideration is required, suggestions for further work are indicated.

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

There was unanimous agreement that, in principle, any Australian requirements should be more closely aligned with international practice through adoption of UK, EU, US or NZ processes/requirements. Many stakeholders pointed out that Australia has already committed to international alignment for clinical trials, as the TGA has adopted the international quality standards CPMP/ICH/135/95 (ICH GCP)2 and ISO 14155. Where a preference was expressed by stakeholders, EU models, approaches or definitions were favoured.

Proposed options:

- Align the Australian safety reporting system with international practice whilst taking into account any Australian regulatory requirements.
- Ensure the Australian framework for safety monitoring incorporates a risk-adapted approach.

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

There was unanimous agreement that the requirements for safety monitoring and reporting in Australia require updating. Many stakeholders did not differentiate between the subgroups outlined in Q.2 but commented that the current system was ‘too burdensome’ or ‘adds little value’. The importance of ensuring that the Australian safety reporting system minimises the prospect of safety issues being missed through inappropriate handling was raised in a number of submissions.

“Review of individual reports or limited sub-sets, such as those arising within Australia, may cause either undue and/or inappropriate concern regarding potential safety signals or, alternatively, mean that safety signals are missed.”

(Pharmaceutical company)

a) Investigators

Stakeholders commented that Section 4 of ICH GCP already adequately defines the safety review and reporting responsibilities of the Principal Investigator and should be better recognised.

“The safety reporting responsibilities of the principal investigator are set out in ICH GCP, and as such, standardised internationally. All reports are sent to the sponsor first. The requirement to follow GCP for clinical trials should be more prominent in NHMRC guidelines.”

(Biotech company)

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2 An annotated version of ICH GCP has been adopted by the TGA.
There was very strong consensus that the investigator’s role could be made much less onerous without compromising patient safety. For example, stakeholders highlighted the burden that processing safety reports places on the Coordinating Principal Investigator (CPI)/Study Coordinator who is required to send correspondence back and forth between the HREC and all other Principal Investigators (PIs) in a multi-centre trial. All but two stakeholders confirmed their support for amending the reporting pathway to enable sponsors to communicate directly with HRECs and in parallel with investigators, in line with European practice.

“The current process puts the investigator at the centre of the communication cascade for Safety Reporting. We consider that this is inappropriate. This responsibility lies best with the trial sponsor as outlined.”

(Pharmaceutical company)

b) Institutions
Some responses acknowledged that an institution’s safety reporting and monitoring role may differ when hosting externally sponsored trials and sponsoring investigator-led/collaborative group trials. Many confirmed that, for both internally and externally sponsored trials, they would wish to receive targeted safety reports and protocol violations, as this was an appropriate means of monitoring impact on medico-legal risk and adherence to contractual obligations. Concerns were expressed regarding the institution’s role as trial sponsor (see Q2.d below).

“For non-industry trials, the term sponsor is not well defined in Australia. Institutions that take on the role of sponsor have very little support and guidance and may not be sufficiently resourced to performing their duties optimally. It is a topic that needs to be addressed… these reforms would provide a convincing argument to have our Network fund infrastructure to truly support the pharmacovigilance and monitoring of investigator driven clinical trials.”

(Hospital Network)

c) HRECs
Much of the feedback from HRECs concerned the relevance of the reports they received, the context in which they are received and also whether HREC members are qualified or have the resources to read and understand the information being sent.

“A culture develops of “report everything” as if the HREC is the “police” in these matters when in fact they are not at all equipped to make these judgements in the absence of any aggregate assessment.”

(HREC)

Stakeholders commented that the HREC’s role in safety monitoring has not evolved since the adoption of the National Mutual Acceptance (NMA) Scheme and therefore, their current role is “a historical artefact” of the previous system. Some also indicated that confusion/duplication in roles and responsibilities between HREC and institution still exists and should be addressed.

d) Sponsor
A number of stakeholders indicated that if HRECs were no longer to receive single case reports, there would be a need for clear and convincing reassurance that sponsors’ systems for safety monitoring are robust and transparent. In particular, concern was raised from both commercial and non-commercial stakeholders over the readiness/ability of smaller or less experienced sponsors to meet the requirements laid down in the quality standards ICH GCP and ISO 14155. One stakeholder commented that HRECs should not only be mindful of a sponsor’s size and general experience with trials, but also their experience with a particular investigational product or type of investigational product.
“If the onus for safety is going to be with sponsors, there needs to be oversight...especially for small companies that may not have the infrastructure to abide by or understand all of the rules and requirements, for example, the writing of IBs (or equivalent) for early phase products/devices.”

(Pharmaceutical Company)

i) Non-commercial trials with more than one sponsor
Institutions and industry called for guidance to clarify how roles and responsibilities for trial safety monitoring and reporting should be assigned. For multi-centre, non-commercial trials that may involve multiple sponsors, it was seen as particularly important to ensure that the HREC was aware of exactly which entity/person was responsible for pharmacovigilance and for communication with the Regulator.

ii) A formalised risk assessment process
In order to address concerns relating to sponsor readiness, stakeholders suggested that Australian practice should more closely align with international guidance\(^3\) by ensuring that a more formalised risk assessment process for clinical trials is developed and promulgated in Australia. Many submissions (particularly those representing non-commercial sponsors) requested further support so that all trial sponsors better understand how to:

- Define the risks and hazards inherent in a clinical trial protocol (when compared with standard care)
- Develop the appropriate risk mitigation plans
- Document the risk assessment process for review by approval bodies*

*The Australian Clinical Trial Alliance’s (ACTA) submission highlighted that the requirement for a risk assessment (either contained within the protocol or in a separate document) could help to expedite governance and ethics assessments by providing reassurance that appropriate risk management plans are in place:

“Many countries have developed a more formalised approach to documenting the risk assessment performed for each clinical trial which includes a simple risk based classification. This allows HRECs and institutions to quickly assess the adequacy of the proposed systems to mitigate additional risks to participants and, where there are no additional risks, to be reassured of that fact.”

(ACTA)

Proposed options
- Ensure the specific responsibilities of the investigator, institution, HREC and sponsor are aligned with international practice including; ICH GCP, ISO14155 and the 2016 EU Clinical Trial Regulation.
- Ensure any new framework places the responsibility for the ongoing safety analysis of the trial with the sponsor.
- Develop documentation and guidance for trial sponsors including guidance on the requirement for a robust and transparent clinical trial risk assessment and risk management plan.
- Amend the reporting pathway to place the sponsor at the centre of the communication cascade in line with European practice, allowing sponsors to report directly to HRECs and to investigators in parallel.

\(^3\) Example include, the OECD Recommendations for Governance of Clinical Trials and the ICH GCP Addendum Business Plan, both of which describe the requirement for an upfront assessment of risk specific to a study design and protocol.
3) Do current arrangements for safety reporting create any barriers to conducting multi-centre clinical trials? How can these arrangements be streamlined?

Two clear themes emerged:

a) Lack of standardisation

The considerable variation in safety reporting practices across Australia was the most commonly cited barrier to conducting clinical trials. This view was strongly expressed by both commercial and non-commercial stakeholders. Many submissions called for standard and well-defined systems to reduce the administrative burden for all sponsors who, at present, have to expend considerable resources interpreting the specific requirements that exist, not only across jurisdictions, but also across individual institutions within each jurisdiction:

“Lack of standardisation in safety reporting requirements increases burden on the Co-ordinating Investigator and is a deterrent for sites to take on this critical role. It also creates a burden on sponsors to confirm compliance with the variety of HREC requirements.”

(Pharmaceutical Company)

b) Confusion and lack of understanding of safety reporting requirements

Another common topic raised by stakeholders was the lack of clarity and understanding that exists in Australia with respect to clinical trial safety reporting. The confusion that has arisen has been compounded by the complex reporting pathways and the variability in requirements across institutions. Some of the responses suggested that this lack of clarity may impact on Australia’s attractiveness as a destination for clinical trials:

“The current arrangements with their ambiguity create barriers to conducting multi-centre clinical trials. Overseas headquarters demand clear reporting guidelines when conducting such trials in Australia or when accepting Australian sites into international multi-centre trials.”

(MTAA)

“The purpose of the current safety reporting processes is often questioned, as to what aspects are ‘productive’ and what are simply ‘ticking the box’."

(Pharmaceutical Company)

The ambiguous reporting responsibilities were seen as, potentially, a direct risk to patient safety.

“Current arrangements are complex, often misunderstood or misinterpreted leading to delays in submitting reports. This may impact on patient safety.”

(State/Territory Response)

Stakeholders called for both a high level overview of the agreed processes and also more detailed guidance that would clarify the required processes. The development of processes where all responsibilities are clearly defined and explained and clear lines of communication are implemented was suggested as an effective way to make safety reporting systems more robust.

Proposed options

- Develop standard reporting procedures and ensure that all requirements are clearly communicated in relevant guidance.
- Ensure the added value of each process or activity is recognised by all parties.
4) What role should the review of single case events play in the monitoring of clinical trials? Are current arrangements appropriate? If not, how should these be changed?

There was very strong agreement that current arrangements for the reporting of single case events are not appropriate, as the present system requires such events to be sent to multiple parties for review/analysis when only the sponsor\(^4\) is equipped to perform a meaningful analysis. In particular, stakeholders confirmed that it was not appropriate for HRECs to review all single case events as this does not contribute to participant safety:

> Optimally, a DSMB should be able to collate and interpret reports and determine whether any responsive action is warranted. However, once a determination has been made and the sponsor has taken the necessary action, it is the outcome (i.e. the protocol and/or PICF amendment, IB revision or other notification) that, as a matter of course, is provided to the HREC for approval. The subsequent submission to the HREC of the individual report regarding the event that prompted the necessary action is therefore redundant and, as a consequence, entirely unnecessary and wasteful…”

(Institution)

Stakeholder also confirmed that it was not appropriate for investigators or institutions to make immediate judgments on whether each single event has any impact on the continued ethical acceptability of the trial.

Proposed option

- Ensure that any new framework places the responsibility for the review of single case events as part of the ongoing safety analysis of a trial with the sponsor.
- Remove the requirement for investigators to make immediate judgements on the continued ethical acceptability of the trial based on single case events.
- Review and rationalise the reporting of single case events to HRECs and institutions to ensure these bodies only receive reports that impact on their roles.

a) Commercial companies with global SOPs that mandate the sending of SUSARs – The use of portals for transmitting safety data

The 2009 Position Statement discouraged the practice of sending single case SUSARs to investigators in an expedited fashion. However, the consultation confirmed that, for some companies, this practice would be hard to amend as a company’s global SOPs may mandate the sending of these SUSARs and occasionally, line-listings. There was a view that, for this to be amended, endorsement would be required from the TGA.

> “The TGA would need to endorse what the rules are. If we can quote ‘legislation’ that prevents us from having to do this, we can ask for an exception”

(US-based Pharma Company)

Some companies (particularly for larger trials) find it cost effective to use portals to communicate safety information to investigators. Each individual who is obliged to access the portal (e.g. PI, trial coordinator) is usually assigned a log-in ID. At present, however, there is considerable variation in practice relating to company policy for the access and review of safety information by site staff. Some companies do not require ‘proof of review’ for routine reports with no safety implications and accept that investigators will access this information as and when they feel it is appropriate. Other companies expect ‘proof of review’ from all sites for each new event/listing that is added to the portal, creating a large burden for both investigators and sponsors to ensure all paperwork is reviewed and filed.

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\(^4\) The sponsor, DSMB and Medical Monitor were all cited as having a role in the analysis of single case events.
“Clarification on whether Investigators are required to provide their assessment of whether SUSARs (individual or line listings) lead to any action on their behalf should be clearly written into revised requirements, so there is no misinterpretation of what is required by the investigators.”

(Pharmaceutical Company)

**Suggestion for further work**

- NHMRC and TGA could jointly consider the acceptability of a system that allows sponsors to differentiate between safety reports that do or do not require ‘proof of review’.

**b) Flexibility for a sub-set of studies**

Some stakeholders suggested that, for a sub-set of trials, there may be a requirement to build additional flexibility into the system for reporting to HRECs.

“For studies which have very short accrual times...a more responsive, flexible approach is needed to ensure findings can be actioned in a timely manner.”

(Cancer Council)

For example, for certain early phase trials combining two phases, an interim report to the HREC before moving on to the next phase was considered necessary. Stakeholders did comment that caution should be exercised with regard to the degree of flexibility as ‘variation in practice’ was highlighted as a major problem with the current system and should be carefully managed in any new system. As such, any flexibility would need to be developed within well-defined parameters.

**Suggestion for further work**

In any reporting framework/pathway that is developed, consider

- Developing guidance that enables institutions to determine the parameters for flexibility in safety reporting requirements for a sub-set of trials on a case-by-case basis.

**c) Institutions’ receipt of single case events**

Responses received from hospital representatives confirmed that knowledge of confirmed\(^5\) single case SUSARs and targeted protocol violations originating from within their institution would be beneficial and would support local risk management practices\(^6\) to:

- Provide knowledge of any event that may lead to a dispute or complaint; and
- Facilitate a longitudinal analysis to determine whether a report arising from one trial has an impact on other trials conducted with the same IP/device or by the same investigator.

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\(^5\) One respondent commented that, for trials with an external sponsor, a SAE that is reported to the sponsor is not assigned as a SUSAR until the sponsor formally confirms the assignment.

\(^6\) Responses confirmed that reporting should be in keeping with organisation-wide reporting of incidents relating to patient safety (e.g. a hospital’s clinical incident reporting system).
Proposed option
- Include the requirement for institutions to consider the need for SUSARs that arise from within the institution to be sent to both clinical and research governance staff for information and risk management purposes as a means to ensure appropriate internal and external reporting of clinical incidents and adverse events.

5) Should reportable protocol violations be aligned with international practices? If not, what alternatives are suggested?
The general consensus from most stakeholders was that alignment with the European practice of sending only serious breaches would be favoured. The sending of all deviations and violations\(^7\) to approval bodies provides no added value and is a drain on resources.

a) Terminology
Most stakeholders agreed that HRECs and institutions should be sent protocol violations that may impact on the conduct of the trial. However, stakeholders cautioned against the use of the term ‘Reportable Protocol Violation’ in any Australian guidance. It was felt that stakeholders’ notion of the definition of protocol violation may be preconceived and a new term would be preferable. ACTA has suggested in their submission that the definition proposed in the consultation paper (which was taken from UK Clinical Trial legislation) be replaced with the Europe-wide definition taken from the 2016 EU Clinical Trial Regulation:

Serious breach of GCP/protocol: A breach likely to affect to a significant degree:
- The safety and rights of a participant or
- The reliability and robustness of the data generated in a clinical trial

b) Handling protocol deviations
Some of the responses received from institutions requested that if protocol deviations were no longer reported individually to HRECs/institutions, they should be reported in the annual progress report to the institution. However this request may have arisen out of confusion over roles for assessing such events. Good Clinical Practice places the responsibility on the sponsor to collate all non-compliances (deviations and violations) and act to secure compliance (ICH GCP 5.20). As such, if the institution is the sponsor, then oversight of all non-compliances is appropriate.

c) Further guidance on serious breaches
Some stakeholders called for clear guidance so sponsors understand how the serious breach reporting process would be managed. Suggested reporting timeframes ranged from 7-15 days. Stakeholders requested that reporting timeframes and definitions be standardised and accepted by all approval bodies.

Proposed options
- Report only violations that impact on participant safety or data credibility to HRECs and institutions and adopt the term Serious Breach of GCP/Protocol.
- Source the definition for Serious Breaches from the 2016 EU Clinical Trial Regulation.
- Develop guidance on Serious Breaches reporting to include timeframes.

\(^7\) There is no internationally accepted definition of protocol deviation or violation; however, protocol deviations are generally considered as less serious examples of non-compliance that do not impact of patient safety or eligibility.
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?

Both the reporting of ‘significant safety issues’ and ‘urgent safety measures’ is a requirement of ICH GCP and TGA guidance. There was acknowledgement from stakeholders that Australian guidance, including the Position Statement, already incorporates the requirement to report significant safety issues. However, stakeholders agreed that more guidance and clarification (including examples to aid understanding of how these reports would be handled) would be beneficial.

European guidelines CT-3 (7.11.4) requires the reporting of ‘safety issues that are relevant to participant safety but do not fall within the definition of SUSAR’, for example, safety findings reported by a DSMB. As these events are not subject to the reporting requirements for SUSARs (i.e. 7/15 day timeframe using a prescribed format), EU legislation provides a reporting framework for the ‘outcomes’ that may arise from significant safety issues.

Significant safety issues may be communicated as:

- **An amendment** – The majority of Significant Safety Issues (SSIs) would be communicated to approval bodies and investigators in the form of an amendment. For example, a revised protocol/PICF or updated IB/PI where the risk benefit assessment is altered.
- **An urgent safety measure** – A deviation from the protocol that is instigated to protect a participant from an immediate hazard (and therefore instigated before approval is sought). Deviations are communicated promptly to investigators and approval bodies via a ‘post hoc’ amendment.
- **A ‘Dear Investigator’ Letter** – Often used by companies to convey new safety information or a call for vigilance, but that may or may not require an amendment.
- **A notification of a temporary halt or early termination of a trial** – Communicated promptly by the sponsor to approval bodies and investigators in parallel.

**Proposed options**

- Adopt the term ‘significant safety issue’ as an overarching term for safety issues that are relevant to participant safety, but do not fall within the definition of a SUSAR.
- Clarify that urgent safety measures, IB/PI updates that alter risk/benefit, ‘Dear Investigator’ letters and temporary/permanent halts are sub-categories of the term ‘significant safety issue’.

7) What role should Line Listings play in safety monitoring for clinical trials?

Line Listings are seen as an important tool for ongoing monitoring of therapeutic goods and as a tool for picking up trends such as a change in nature, severity or frequency of expected adverse reactions. However, the majority of stakeholders commented that HRECs and investigators are not equipped to perform this analysis and would be better served receiving the sponsor’s analysis of the Line Listing rather than the raw data itself. Some stakeholders commented that the only value of Line Listings to HRECs would be to demonstrate that an appropriate sponsor review has taken place, however, others felt that as long as sponsors were able to sufficiently outline their review process to HRECs, this would be sufficient.

“A simple report from Sponsor outlining the review process for all events and the outcome decisions of the review should be the only document required for local submission.”

(Hospital Network)

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8 The TGA already exercises some oversight by requiring all sponsors to keep detailed records of all adverse events and reactions in tabulated format to be provided to the TGA on request (Access to Unapproved Therapeutic Goods).
Suggestion for further work

- In any reporting framework/pathway that is developed, consider whether Line Listings should still be routinely sent to HRECs or institutions, or, alternatively, remain solely as part of the sponsor’s processes for detecting safety issues.

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?

Questions 8 and 9 are considered together as most responses combined comments relating to the requirement for annual safety reports (ASRs) and the submission of Developmental Safety Update Reports (DSURs). The majority of stakeholders felt that annual safety reporting processes could be improved through provision of further guidance covering a range of topics:

a) Clarification of the Purpose of the Annual Safety Report (ASR)

Some submissions identified that, internationally, the purpose of the ASR differs from other safety communications. Whereas most communications to approval bodies are submitted to transmit the ‘outcomes’ of safety analyses, the ASR’s main objective is to provide an overview of the previous year’s analysis to reassure HRECs that the sponsor has been adequately monitoring and evaluating the evolving safety profile of the investigational product. For example, providing information to the HREC confirming that the timing/frequency of DSMB meetings were in accordance with the protocol was considered appropriate.

“HRECs need to be reassured that safety monitoring is occurring and this should be commented on in the annual report.”

(HREC)

b) ICH E2F - Development Safety Update Report (DSUR)

Stakeholders indicated that alignment with international practice, by adoption by commercial pharmaceutical companies of the DSUR format for annual safety reports, would be a useful outcome. However, there was some debate as to what components of the DSUR would be appropriate for HRECs to receive, as current practice varies. The international DSUR guidance, ICH E2F states:

“The DSUR is intended to serve as an annual report to regulatory authorities. Where national or regional laws or regulations require submission of an annual safety report on an investigational drug to ethics committees/institutional review boards, the DSUR Executive Summary might be appropriate, supplemented with line listings of serious adverse reactions (SARs) as warranted.”

ICH E2F confirms that the full submission of a DSUR to HRECs is not necessary. It also does not mandate the sending of Line Listings, particularly if HRECs do not have the resources to assess them.

c) ASRs for sponsors who do not have access to DSURs

Whereas the DSUR was considered appropriate for commercial pharmaceutical companies who have access to them, most stakeholders cautioned that rigid guidelines for format and content (particularly for non-commercial trials) should be avoided. A more risk-based approach was favoured. Some submissions commented on the suitability of the New Zealand HDEC guidance which requires sponsors to provide a concise report, written in lay language, and which includes:

For medical devices please see Q 14 and 15 for a discussion of ASR requirements.
• a brief description and analysis of new and relevant findings that may have a significant impact on the safety of participants
• a brief analysis of the safety profile of the new medicine and its implications for participants, taking into account all safety data as well as the results of any relevant non-clinical studies
• a brief discussion of the implications of safety data to the risk-benefit ratio for the intervention study, and whether study documentation has been or will be updated
• a description of any measures taken or proposed to minimise risks (where such measures would be an amendment, it should be for review in the normal way).

Some stakeholders commented that a brief summary supplied with an updated investigator’s brochure may fulfil the requirement for the Annual Safety Report.

d) Sending ASRs to Investigators (maintenance of the blind)
Some commercial stakeholders specifically commented on the requirement to send the ASR to investigators:

“Currently, as a Sponsor, we provide the DSUR to our investigators only in order to meet the requirements of the current NHMRC Position Statement”

(Pharmaceutical Company)

Consideration for ‘maintenance of the blind’ was cited as one reason why ASRs should not be sent to investigators as they contain ‘unblinded’ data. The 2016 EU Clinical Trial Regulation advises that investigators should remain blinded unless the process of unblinding of/by the investigator is relevant to patient safety. In general:

“...the blind shall be maintained for other persons responsible for the ongoing conduct of the clinical trial (such as the management, monitors, investigators) and those persons responsible for data analysis and interpretation of results at the conclusion of the clinical trial, such as biometrics personnel.”

2016 EU CT Regulation (2.5.19)

e) Annual progress reports
There was some confusion as to whether the proposed annual safety report would replace the current progress report to HRECs/institutions or whether it would be in addition to that report. Internationally, both are sent to (H)RECs for clinical trials of investigational medicinal products. New Zealand guidance suggests:

• For clinical trials, the annual safety report is appended to the progress report.
• Where desirable, the first annual progress report may be submitted early, in order to align with annual reporting cycles for the study in other countries.

Proposed options
• Replace six monthly line listings with an annual safety report to HRECs.
• Ensure that any reports to HRECs allow confirmation that the sponsor is adequately monitoring the trial’s risk/benefit ratio in accordance with their safety monitoring plans, and that those plans remain adequate.
• If sponsor have access to the DSUR, recommend that only the DSUR Executive Summary is sent to HRECs.
• Remove any requirement for annual safety reports to be sent to investigators.
Suggestion for further work
In any reporting framework/pathway that is developed consider
• Reviewing the format and content of the ASR for sponsors who do not have access to the DSUR.

10) Would it be beneficial to have guidance on how and why the ‘expectedness assessment’ should be undertaken?
A few commercial companies called for further guidance on how the ‘expectedness assessment’ should be undertaken. Some acknowledged the use of the term ‘reference safety information’ which describes the section of the investigator’s brochure/product information that contains a list of expected serious adverse reactions. Some commercial companies commented that their global pharmacovigilance departments were responsible for this assessment, so guidance would not be required. However, stakeholders sponsoring non-commercial trials did request further guidance as they did not feel that the current framework clarified the importance of this assessment\(^\text{10}\) that they would have to perform. Guidance would help ensure that SUSARs are appropriately and consistently identified in Australian clinical trials.

“The ACTA believes that the terms, ‘unexpected adverse reaction’ and ‘reference safety information’ should be clearly defined in Australian guidance.”

Suggestion for further work
In any reporting framework/pathway that is developed, consider
• Developing guidance for sponsors on the expectedness assessment and promulgation of terms associated with this activity in conjunction with the work on standard terminology (Q.11).

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?
There was universal agreement amongst stakeholders that standardisation of reporting terminology was required.

“The conduct of clinical research is complex and this complexity is compounded by the need to involve a number of different individuals with a variety of expertise. It is important therefore to ensure that clear guidance is produced so that all those required to implement activities for clinical trials understand the purpose of each activity, its value and also the scope and extent of their responsibilities.

We therefore support the suggestion that standard definitions are promulgated through updated guidance. It is also suggested that appropriate training is provided to all stakeholders who are required to understand these complex requirements and the roles and responsibilities of all stakeholders are re-clarified once any changes that come about are put in place.”

(ACTA)

Stakeholders agreed that Appendices 2 and 3 in the discussion paper\(^\text{11}\) were a good basis to begin to develop a standard set of terminology\(^\text{12}\). One pharmaceutical company also suggested it would be prudent to investigate whether TransCelerate\(^\text{13}\) were doing any work on standard terminology.

\(^{10}\) The expectedness assessment is one of the three assessments required to confirm whether a SUSAR has occurred.


\(^{12}\) The response from the medical device sector was that ISO 14155 should be used as the source for standard terminology.

\(^{13}\) TransCelerate BioPharma Inc. is a non-profit organization focused on advancing innovation in research and development (R&D).
Stakeholders also advised that any proposed terminology and definitions should be peer reviewed before being widely adopted as the data dictionary for Australia.

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<tr>
<td>In any reporting framework/pathway that is developed, consider</td>
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<td>• A wider consultation on standardisation of terminology to include the definitions for the terms discussed in Q.5, Q.6 and Q.10.</td>
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12) **What further guidance is required for HRECs/sponsors about how DSMBs should operate?**

Both commercial and non-commercial stakeholders indicated that they would welcome further guidance on the operation of DSMBs. However some stakeholders, particularly those involved in non-commercial trials, also requested guidance on alternative safety monitoring options when a DSMB was not appropriate for the study being conducted.

a) **Data & Safety Monitoring Board Guidance**

Many stakeholder groups recommended that better guidance on the use and operation of DSMBs be produced to help sponsors and HRECs perform their roles. Important issues/components to address in any guidance might be:

• What is a DSMB?
• The responsibilities and functions of the DSMB
• How DSMBs should operate (including a sample pro forma)
• Guidance for institutions on how to establish a DSMB (or a panel of truly independent experts which could be utilised for investigator-led studies)
• A risk assessment matrix to assist both sponsors and HRECs to determine when a DSMB is required and, if not required, what alternative safety monitoring arrangements may be appropriate
• A sample charter/terms of reference that can be provided to sponsors
• Appropriate membership of a DSMB and how to determine independence
• How and when to convene an independent DSMB or other type of independent safety monitoring
• Courses for DSMB members and independent medical monitors

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<td>In any reporting framework/pathway that is developed, consider</td>
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<td>• Developing guidance on DSMBs and alternative safety monitoring arrangements to assist sponsors to develop appropriate, risk-based safety monitoring plans.</td>
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13) **Do the proposed simplified reporting arrangements outlined in Appendix 6 (of the consultation paper) represent an acceptable approach to how safety monitoring and reporting could occur in Australia? If not, what would be an alternative approach?**

Many stakeholders supported the model unequivocally. The remainder, supported the proposed simplified arrangements ‘in principle’ with provisos or minor amendments. Some endorsements also requested clarification of the information that must be reported to approval bodies. Two responses supported reporting in line with the proposed simplified arrangements, but through the principal investigators rather than directly from sponsors.

a) **Endorsement by NHMRC and TGA**

A number of stakeholders (particularly global commercial companies) stressed that any new framework would require specific endorsement from both the NHMRC and the TGA.
“Endorsement by the appropriate bodies will be essential to allow these changes to be implemented across the board. TGA endorsement would be beneficial. The requirements should be clearly articulated and documented, and withstand any audit or inspection by external Regulatory agencies…”

(Pharmaceutical Company)

The response from the TGA also indicated that the proposed simplified approach appeared to be reasonable, which shifts more of the responsibility onto the Sponsor, who would be better placed to aggregate/analyse safety events. However, the TGA also stressed that some modification was required to ensure that the sponsor reported urgent safety measures, premature terminations/halts to the TGA.

### Suggestion for further work
- Ensure that any revision to the safety monitoring and reporting framework is agreed and endorsed by both TGA and the NHMRC.

### b) Filing requirements for safety reporting documentation

Commercial companies employ considerable resources confirming that safety reports are filed by all principal investigators. Some stakeholders commented that current filing requirements should be reviewed, as some of the current requirements do not reflect the move to a single ethical review model. For example, one large CRO suggested that it would be useful to clarify whether all principal investigators would need to file all communication between the sponsor/CPI and the HREC. It was suggested that PIs should only be required to receive and file documentation that is relevant to their role and that helps reconstruct the conduct of the trial at their site.

“Clarification and standardisation of required documentation by all parties would be beneficial. Standards for documentation of receipt/review/acknowledgement (by investigator /HREC/ Institution) of safety information and clear guidance on who is required to have this documentation as part of their Trial Master File would allow significant improvement in the process of safety reporting.”

(Pharmaceutical Company)

### Proposed option
- Develop simplified arrangements for safety reporting, taking into consideration Appendix 1, for inclusion in any future guidance.

### Suggestion for further work
- Consider further discussion between the TGA and the NHMRC to ensure that any revision to the safety monitoring and reporting framework is agreed and endorsed by both bodies.
- Consider further discussion between the TGA and the NHMRC to clarify filing requirements for safety reporting documentation.
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?

The most significant response received from the medical device stakeholder group was from the Medical Technology Association of Australia (MTAA) which confirmed that, in the majority of areas, medical devices trials could follow the same systems as those used for investigational products. The MTAA did suggest that a separate version of simplified reporting arrangements be produced to reflect the differing terminology (SADE v SAR and USADE v SUSAR and CIP v protocol).

“The proposed simplified reporting arrangements provide an acceptable outline. However the specifics of ISO 14155 should be taken into consideration as well”

(MTAA)

All other stakeholders who responded to Q.14/15 provided similar feedback. One additional consideration was identified:

- Annual Safety Reporting for Medical Device Trials
  Table E.2 of ISO 14155 discusses ‘interim or annual reports to ethics committees. However, the MTAA and other device stakeholders confirmed that there is no clear guidance relating to the requirement for annual safety reports for medical device trials. Therefore, there is a need to consider whether provision of these ASRs to HRECs would add any value to HRECs.

**Proposed options**
- Develop simplified safety reporting arrangements using Appendix 1 as the basis to give further consideration to areas such as annual safety reporting.
- Ensure the framework takes into account device specific adverse events and device deficiencies. Terminology and requirements should be sourced from ISO 14155.

5. Summary

This NHMRC consultation explores whether there is a need for further alignment with international safety monitoring practices and whether this would improve the efficiency of the Australian safety monitoring and reporting system.

The feedback from this consultation confirmed that the trial sponsor (rather than the HREC or institution) is best placed to perform the analysis of all safety reports in order to determine whether any changes to the risk/benefit assessment has occurred. There was overwhelming consensus that HRECs and institutions cannot perform an adequate analysis of the raw data, so that their review of these data does little to improve the safety of participants in clinical trials. Therefore, removing this requirement would not make the Australian system any less safe. However, in order to improve the current system, consideration could be given to:

1) Provision of considerable support and guidance for less experienced sponsors to ensure their pharmacovigilance systems are compliant with ICH GCP or ISO 14155. One key component of this work would be a new risk assessment process which would help sponsors identify the risks in their trials and implement appropriate risk mitigation plans. A documented risk assessment would also help HRECs better assess the adequacy of the sponsor’s proposed systems to mitigate risks.
2) Ensuring Australian guidance more closely aligns with international practice and enables the efficient
communication of key safety issues, such as the reporting of significant safety issues.

3) Ensuring Australian guidance reflects that as the trial progresses, the HREC receives safety
information for two distinct reasons:
   - To assess whether any risk/benefit changes reported by the sponsor have an impact on the
     continued ethical acceptability of the trial and to confirm whether any changes are adequately
     reflected in trial documentation (e.g. protocols and participant information documents).
   - To be reassured that the sponsor is monitoring the trial in accordance with the safety monitoring
     plans described in the protocol or risk assessment and that those plans remain adequate.

4) Ensuring that any new system recognises that institutions require targeted safety information from
their site PIs in order to monitor institutional risk so that there are mechanisms in place to withdraw
project authorisation if those risks become unacceptable.

5) Ensuring there is a common understanding of all requirements.

The feedback from this consultation confirmed strong support for further work to address the lack of
standardisation across Australia and the lack of clarity associated with the current system. The
introduction of national standard safety reporting processes (including standard definitions) and the
development of clear and consistent Australian guidelines for these processes was considered a priority.

It is anticipated that further consultation to refine the new framework with a clear explanation for each
change in practice will ensure the system is accepted and understood and that all parties recognise the
added value of each reporting requirement or process.
Significant Safety Issues (reported as USMs, DILs, IB/PI Updates, Premature Termination/Temporary Halt)

Urgent Safety Measures

SUSARs (if required by sponsor’s SOPs)

SPONSOR*
(Oversight from DSMB or alternative)

TGA

SUSARs (Australian Sites)
Significant Safety Issues (reported as USMs, DILs, IB/PI Updates, Premature Termination/Temporary Halt)

INVESTIGATOR
(CPI*** or PI)

INSTITUTION

Significant Safety Issues (reported as USMs, DILs, IB/PI Updates, Premature Termination/Temporary Halt)

SUSARs** and Serious Breaches of GCP/Protocol arising from the local PI site

Key:
AE - Adverse Event
SAE - Serious Adverse Event
SUSAR - Suspected Unexpected Serious Adverse Reaction
DILs - Dear Investigator Letters
USM - Urgent Safety Measure

IB - Investigator’s Brochure
PI - Product Information
PI - Principal Investigator
CPI - Coordinating Principal Investigator
SOP - Standard Operating Procedure
HREC - Human Research Ethics Committee

*For investigator-led/CRG trials, the CPI may take on the sponsor’s responsibility for the notification of information to the TGA, HREC & investigator
** Once assignment has been confirmed by the sponsor
*** The CPI is copied in to all correspondence sent to the PI and HREC
N.B. A reporting pathway using terminology from ISO 14155 would be required for medical device trials