Australian Clinical Trials Alliance

NHMRC consultation paper on updating arrangements for safety monitoring and reporting of clinical trials in Australia

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Thank you for the opportunity to comment on possible reforms to the way in which safety monitoring and reporting is conducted in Australia on behalf of the Australian Clinical Trials Alliance (ACTA) – a community of 60 different networks representing more than 10,000 clinicians and researchers who collaborate to conduct vital 'public good' clinical research within the Australian healthcare system (see appendix A).

We applaud the NHMRC for initiating this review and believe the discussion paper clearly captures the issues that are endemic in the Australian safety reporting system. In particular we are pleased to see that this document identifies that strict adherence to some of the provisions in the ICH GCP are not necessarily suitable for public good trials, specifically those that are classified as comparative effectiveness studies and that do not require registration through the CTN or CTX scheme.

The consultation document importantly highlights the international perspective, which identifies the problem with HRECs being involved in urgent safety reporting pathways. It is ACTA's view that the current involvement of HRECs is a historical artefact and that with the implementation of effective governance in institutions there is no longer a role for the HREC in reviewing individual Adverse Events (AEs) or Serious Adverse Events (SAEs).

Overall, ACTA believes that the NHMRC's principal objective from this review should be to create a 'minimal acceptable safety standard' for clinical trials in Australia that:

I. makes the safety of subjects its first concern,
II. harmonises with international (ICH) standards,
III. is consistent across all states and territories of Australia (and New Zealand),
IV. removes burdensome reporting requirements which do not improve safety, and
V. provides a responsible and compliant alternative reporting pathway for AEs which does not involve HRECs.

We hope our comments are useful for achieving this goal.

Consultation Questions

General

1. Should Australian guidance for safety monitoring and reporting be aligned with International practices?

If yes, what key information should be adopted?

Many of the current practices for safety reporting in Australia create an unnecessary resource burden without enhancing participant safety. In particular, significant inconsistencies between institutions mean that compliance can be very difficult for multicentre studies. ACTA submits that alignment with international practice in the area of safety reporting should take place to promote harmonisation. Many of the networks affiliated with ACTA involve international collaboration and consistency across jurisdictions will be very helpful.

Australia has already committed to aligning with international clinical trial practice by adopting as mandatory under the Therapeutic Goods Act 1989, the quality standards developed by the International Conference on Harmonisation (ICH) and the International Organization for Standardization (ISO). These quality standards and are recognised as benchmark standards throughout the world.

However, ACTA considers that it is important that the TGA comment makes the provisions in the ICH mandatory for all trials here in Australia. The Europeans have never make ICH GCP 'law', as it was only developed for trials where data are being submitted to regulatory authorities and not for public good trials. Instead in Europe, all trials must work to the core principles of GCP, which is a reasonable expectation and much more achievable for academic trials.

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?

Our recommendations are as follows:

a) Investigators

- Investigators should not routinely comment on the continued ethical acceptability of trials based on single case events and should work to Section 4.11 and 4.3.2 of ICH GCP, which defines their safety review and reporting responsibilities.
- The burden of processing safety reports to HRECs should be removed from the investigational site.
- Investigators should not receive individual Australian and international SUSARs but rely on the sponsor's update of IBs (or PIs). New IB helps to ensure that the most up to date safety information is available to the investigator on the use of the IP in the trial.

b) Institutions

In Australia, the entity that is named as the 'sponsor' for investigator-led trials is often the employing institution of the Coordinating PI. As such, ACTA believes that Australian guidance should acknowledge the differing roles performed by institutions for safety monitoring and reporting as they either 'host' externally sponsored trials or 'sponsor' investigator-led trials/collaborative group trials.

ACTA suggests that where institutions are taking on the role of sponsor, it should be left to the institution to prescribe (through internal SOPs) how the sponsor's responsibilities are executed.

Institutions should not be required to review all individual case safety reports. However, ACTA agree with the UK practice of ensuring that SUSARs from the local site are provided to institutions for 'information purposes'. Institutions would also benefit from receiving 'targeted' information on protocol violations as described in the paper.

Institutions should also receive any information that may impact on the continued governance approval and we suggest that the proposal in Appendix 6 of the discussion paper would meet these requirements.

c) HRECS

HRECs should not be involved in the analysis of safety reports so should not receive any single case reports, including SUSARs. During the approval process, they should reassure themselves that the sponsor's plans for the ongoing safety analysis of the investigational product are proportionate to the risks and complexities of the trial.

d) Sponsors

ACTA would support the following:

I. Formalised risk-based classification of clinical trials.

Many countries have adopted 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.*

** For trials that may pose 'no higher risk than standard medical care' (e.g. 'usual care trials' where the Investigational Product is used within its marketing authorisation or where the use is evidence based and supported by published scientific evidence on safety and efficacy) this approach could be utilised to foster a more proportionate approach to risk in clinical trials.*

II. Direct communication between the sponsor and HREC.

ACTA supports the proposal for sponsors to send all safety reports directly to HRECs and investigators for both commercial and non-commercial trials. All communication should be electronic.

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

The considerable variation in safety reporting practices across Australia is most definitely a barrier to conducting clinical trials. In order to ensure a truly efficient and workable environment for clinical trials, there has to be a much greater level of interoperability. This will 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. We provide an example of the current inconsistencies with kind permission of Barwon Health (Appendix B).

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?

This paper clearly illustrates the divergence between Australian practice and international practice relating to the sending of SAEs to approval bodies. Countries that work to ICH GCP should recognise that the ultimate responsibility for the ongoing safety of an investigational product lies with the sponsor and all individual case reports must be collated by the sponsor. HRECs only receive safety reports for sites for which they are responsible (a partial dataset). In addition, the data is being reviewed out of context.

ACTA considers that even if these reports were informative, which they are not, HRECs do not have the resources to perform a review of these reports.

ACTA agrees with the revised New Zealand Guidelines published in August 2014 which have removed the requirement for investigators to submit individual reports of serious adverse events (SAEs/SUSARs and six monthly line-listings) to HRECs and replaced this with an annual safety report (note that an updated IB is one way that this could be fulfilled).

ACTA also agrees with revised FDA Guidelines which clearly articulate that attempting to review and evaluate these reports (SAEs) without the necessary context is a drain on resources for investigators and HRECs, diverting them from other activities.

Importantly, ACTA suggests that the current system may in fact increase the possibility that important safety issues may be missed due to an effect of ‘white noise’ created by a very large amount of information having to be processed by organisations that are not suitably resourced or capable of dealing with it.

Protocol Violations

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

Yes, ACTA believes the reporting of all protocol deviations and violations to HRECs and institutions should be stopped as most of these reports provide no added value and are therefore a drain on resources. We believe that Australian guidance should align with the European practice; only reporting to HRECs and institutions violations that meet the definition of a *Serious Breaches of GCP or the Protocol* as outlined in the paper. We also suggest that the term 'serious breach' is more suitable than 'protocol violation' as the stakeholders' notion of the definition of protocol violation may be preconceived.

ACTA supports the use of the EU 2016 version of a 'breach', defined as:

> *"A breach likely to affect to a significant degree:*
> *a) The safety and rights of a participant*
> *b) The reliability and robustness of the data generated in a clinical trial"*

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?

Yes, ACTA suggests that the current guidance needs to be revised and to be made more explicit in recognising that there are better mechanisms (than individual case reports) to ensure HRECs and institutions are informed of anything that may impact on the continued ethical acceptability or conduct of a trial. As indicated in Appendix B, institutions in Australia require expedited reporting to HRECs that do not appear to serve any useful purpose.

Line Listings

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

None. Once again, Australia should consider adopting international practice and move to annual safety reports (see below). HRECs usually do not have the resources to review line listings.

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?

ACTA agree that Australia should align with international practice. The annual safety report should provide the HREC with an annual review and evaluation of safety information in order assure the committee that the safety profile of the intervention is being adequately monitored. An updated IB may fulfil this requirement.

We believe a risk-adapted approach to annual safety reporting is appropriate. Therefore for public good trials we suggest that guidance similar to New Zealand's should be produced for Australia. A simple, concise description of the evolving safety profile of a trial would best serve HRECs.

While we do not support a rigid guidance on the format and content of ASRs, the following general guidance (taken from the New Zealand SOPs) would be useful to HRECs and sponsors:

> *"…Written in lay language, and include:*
> *1.1. a brief description and analysis of new and relevant findings that may have a significant impact on the safety of participants*
> *1.2. 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*
> *1.3. 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*
> *1.4. a description of any measures taken or proposed to minimise risks. (Where such a proposed measure would be a substantial amendment, it must be submitted to the HDEC for review in the normal way.)"*

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?

We agree with New Zealand guidance that states:

> *"Summaries of safety information such as Development Safety Update Reports may serve as annual safety reports to HDECs provided that they contain the information outlined above. These summaries should usually be accompanied by comment from the CI of the study in New Zealand."*

Expectedness Assessment for Adverse Reactions

10. Would it be beneficial to have guidance on how and why the 'expectedness assessment' should be undertaken?

ACTA believes that the terms, 'unexpected adverse reaction' and 'reference safety information' should be clearly defined in Australian guidance. Guidance should prescribe how and why the expectedness assessment is performed so that SUSARs are appropriately and consistently identified in Australian clinical trials.

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?

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.

Suggested source: Appendix 3 and 4 of this consultation paper could be used as the basis for a document containing standard terminology. However, we believe the following amendment could be made:

- Reportable Protocol Violations – This term may be better defines as a Serious Breach of GCP or the protocol to align with international terminology.

Guidance around Use of DSMBs

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

ACTA appreciates that if the NHMRC supports the proposal that HRECs not receive individual safety reports then more clear guidance should be provided on how these are to be managed. We suggest that more clear guidance is required around section 3.3.20 of the National Statement, specifically:

- What is a Data Safety and Monitoring Board (DSMB)?
- What is the role and function of a DSMB?
- What trials require a DSMB?
- Does the DSMB need to be independent?
- How often should interim safety and efficacy of data be monitored?
- What should be covered in a trial's risk assessment?
- If a DSMB is not convened, what alternative safety monitoring arrangements may be appropriate?

We believe that the trial protocol should define clearly which AEs are to be reported, to whom, and on what time lines - and which are not. As a general rule, AEs should be reported to a DSMB according to ICH guidelines and timelines for multi centre studies, blinded studies and studies carrying significant risk. The membership and operating guidelines of the DSMB, including frequency of meeting, should be spelt out in the protocol

For trials that will not have a DSMB, AEs should be reported according to ICH guidelines and timelines to an independent medical monitor (IMM), who should not be a member of the trial steering committee. The name and responsibilities of the IMM should be spelt out in the protocol, including the actions she or he is expected to take if a significant safety signal is recognised. We note that reporting of SAEs and AEs solely to the trial steering committee is unacceptable because of the potential for conflict of interest

There is a related issue of training for members of DSMBs and for IMMs that was not canvassed in the consultation document or the submission. Clinical trial methodology in general, and pharmacovigilance in particular is not taught well – or at all – in clinical training for physicians and other HCPs. The NHMRC, the Australian Health Ethics Committee or some other appropriate body should consider offering short courses in this area.

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?

ACTA supports the proposal presented in Appendix 6 of the consultation document.

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.

ACTA believes that there is no reason that the safety reporting for devices should differ to those of other clinical trials with the sole proviso that devices may not be readily removable (orthopaedic prosthesis, heart vales/VADs etc.) and may therefore need to be monitored for much longer than drug trials.

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

Besides possible extended time frames ACTA is not aware of any safety issues that are specific to devices that are not the case for drug trials.

Appendix A. Members of the ACTA Community

1. Australasian Child and Adolescent Obesity Research Network (ACAORN)
2. Australasian College for Emergency Medicine Clinical Trials Group (ACEM Clinical Trials Group)
3. Australasian Consortium of Centres for Clinical Cognitive Research (AC4R)
4. Australasian Gastro-Intestinal Trials Group (AGITG)
5. Australasian Kidney Trials Network (AKTN)
6. Australasian Lung Cancer Trials Group (ALTG)
7. Australasian Radiopharmaceutical Trials Network (ARTnet)
8. Australasian Sarcoma Study Group (ASSG)
9. Australasian Sleep Trials Network (ASTN)
10. Australasian Society for Infectious Diseases Clinical Research Network (ASID CRN)
11. Australasian Stroke Trials Network (ASTN)
12. Australia & New Zealand Breast Cancer Trials Group (ANZBCTG)
13. Australia & New Zealand Neonatal Network (ANZNN)
14. Australia & New Zealand Society of Cardiac & Thoracic Surgeons (ANZSCTS) National Cardiac Surgery Database
15. Australia New Zealand Gynaecological Oncology Group (ANZGOG)
16. Australian & New Zealand Children's Haematology/Oncology Group (ANZCHOG)
17. Australian & New Zealand College of Anaesthetists Clinical Trials Network (ANZCA Clinical Trials Network)
18. Australian & New Zealand Intensive Care Society Centre for Outcomes & Resource Evaluation (ANZICS CORE)
19. Australian & New Zealand Intensive Care Society Clinical Trials Group (ANZICS CTG)
20. Australian & New Zealand Melanoma Trials Group (ANZMTG)
21. Australian & New Zealand Musculoskeletal Clinical Trials Group (ANZMUSC)
22. Australian & New Zealand Urogenital & Prostate Cancer Trials Group (ANZUP)
23. Australian Epilepsy Clinical Trials Network (AECTN)
24. Australian Motor Neuron Disease Registry (AMNDR)
25. Australian Neuromuscular Network (ANN)
26. Australian Orthopaedic Association National Joint Replacement Register (AOANJRR)
27. Australian Paediatric Research Network (APRN)
28. Australian Primary Care Research Network (APCReN)
29. Australian Research Centre for Health of Women & Babies, Robinson Institute.
30. Bi-national Colorectal Cancer Audit (BCCA)
31. Burns Service of Western Australia
32. Centre for Anaesthesia & Cognitive Function
33. Centre for Biostatistics & Clinical Trials (BaCT)
34. Cooperative Trials Group for Neuro-Oncology (COGNO)
35. Multiple Sclerosis Research Australia Clinical Trials Network (MSRACTN)
36. Neuroscience Trials Australia (NTA)
37. NHMRC Clinical Trials Centre (NHMRC CTC)
38. NSW Better Treatments 4 Kids (BT4K)
39. Orygen Youth Health Research Centre
40. Paediatric Research in Emergency Departments International Collaborative (PREDICT)
41. Paediatric Trials Network Australia (PTNA)
42. Palliative Care Clinical Studies Collaborative (PaCCSC)
43. Perinatal Society of Australia & New Zealand IMPACT Collaboration
44. Primary Care Collaborative Cancer Clinical Trials Group (PC4)
45. Prostate Cancer Clinical Quality Registry
46. Psycho-oncology Co-operative Research Group (PoCoG)
47. Queensland Centre for Mental Health Research
48. Queensland Clinical Trials & Biostatistics Centre
49. School of Public Health & Preventative Medicine, Monash University
50. South Australian Health & Medical Research Institute (SAHMRI)
51. Spinal Cord Injury Network (SCIN)
52. The ASPREE Study Group
53. The George Institute for Global Health
54. Trans-Tasman Radiation Oncology Group
55. Transfusion Research Outcomes Collaborative (TORC)
56. Type 1 Diabetes Clinical Research Network (T1DCRN)
57. Victorian Ambulance Cardiac Arrest Registry
58. Victorian Cardiac Outcomes Registry (VCOR)
59. Victorian Cervical Cytology Registry (VCCR)
60. Victorian State Trauma Outcomes and Monitoring Registry (VSTORM)

Appendix B. Ethics reporting requirements across six sites in Victoria*.

Item Type	Non-SERP Study (Local HREC Requirements)	SERP Study (Local RGO Requirements)	Alfred Hospital Ethics Committee	Austin Health HREC	Melbourne Health HREC	Peter MacCallum Cancer Centre Ethics Committee	St Vincent's Hospital (Melbourne) HREC D
SAEs Occurring at a site for which Barwon Health (BH) is responsible and which are possibly, probably or definitely related to participation in the clinical trial.	Report within 24 hours of the investigator becoming aware of the event using the appropriate proforma.	Report within 24 hours of the investigator becoming aware of the event using the appropriate proforma	These must be reported to the Alfred Ethics & Research Governance Office within 72 hours of knowledge of the event. All reports should be submitted on an appropriate adverse event form and must include sufficient information and context.	Please submit 1 electronic copy ONLY with electronic signatures where possible in PDF format to ethics@austin.org.au (with the relevant report completed)	All 'related' serious adverse events should be submitted for review within 24 hours of the event or as soon as possible thereafter. An Adverse Event Report form is to be submitted with each report requiring notification to a Melbourne Health HREC. Please submit this form in hardcopy and email to: Hardcopy: Level 6 East, The Royal Melbourne Hospital – City Campus, Grattan Street, Parkville Victoria 3050 Email: research.directorate@mh.org.au	Individual AE or SAE and individual SUSAR or USADE events that have occurred at a site that is required to report to the Peter Mac Ethics Committee as the reviewing HREC must be submitted only if the information materially impacts on the continued ethical acceptability of the trial or requires or indicates the need for a change to the trial protocol, including changed safety monitoring in the view of the investigator or sponsor. Submit promptly - within 24 hours of becoming aware of the event.	All potentially related, possibly related and definitely related SAEs involving patients at the sites listed on the ethical approval letter issued by St Vincent's Hospital All SAEs or SUSARs which impact upon the continued ethical acceptability of the trial (including that which requires or indicates the need for a change to the trial protocol, including changed safety monitoring in the view of the investigator or sponsor) must be reported to the HREC and Sponsor as soon as possible. Since 01/07/2014 they are asking for a more detailed outline of the event, the action taken and the outcome before they will review the SAE. The PI determination of relationship also has to be justified i.e - why the PI feels it was unrelated to the IP. This can be added as a narrative in the description of event field of the DoH forms. They would also prefer one notification for the initial and follow up SAE (not in-keeping with 24 hours reporting guidelines).
SAEs Occurring at a site for which BH is responsible and there is NO impact or NO relationship as determined by the PI/SUB	Do not report to HREC File in the participant research file	Do not report to RGO File in the participant research file	No noted change from above requirements.	No noted change from above requirements.	Not required to be submitted.	Not required to be submitted.	Not required to be submitted.
PATIENT DEATH Occurring at a site for which Barwon Health (BH) is responsible, regardless of relationship to the clinical trial.	Report within 24 hours of the investigator becoming aware of the death using the appropriate proforma	Report within 24 hours of the investigator becoming aware of the death using the appropriate proforma	No noted change from above requirements.	Please submit 1 electronic copy ONLY with electronic signatures where possible in PDF format to ethics@austin.org.au (with the relevant report completed)	No noted change from above requirements.	No noted change from above requirements.	No noted change from above requirements.

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OTHER EVENTS Any event not covered by the above including protocol defined endpoints.	Report to the HREC ONLY if it impacts on the research and action is planned, or there are ethical implications. Use the appropriate proforma.	Report to RGO ONLY if it impacts on the research and action is planned, or there are ethical implications. Email advice	No noted change from above requirements.	Please submit 1 electronic copy ONLY with electronic signatures where possible in PDF format to ethics@austin.org.au (with the relevant report completed)	No noted change from above requirements.	Investigator Alerts and all other forms of safety reporting for projects that are required to report to the Peter Mac Ethics Committee as the reviewing HREC must be submitted only if it is deemed to require urgent action or materially impacts on the continued ethical acceptability of the trial in the view of the investigator or sponsor. The submission must include a memo that: provides explanation of the implications for participants and the conduct of the study states what action is recommended to be taken	No noted change from above requirements.
SADE (Serious Adverse Device Event) INCIDENTS Occurring at a site for which Barwon Health (BH) is responsible and involving actual/potential harm to a patient / caregiver.	Report within 24 hoursReport incidents to the OfR who should coordinate reporting to external organisations, such as the supplier of the device and the TGA.Further advice and forms found at:http://www.tga.gov.au/safety/problem-device-iris.htm#device	Report within 24 hoursReport incidents to the OfR who should coordinate reporting to external organisations, such as the supplier of the device and the TGA.Further advice and forms found at:http://www.tga.gov.au/safety/problem-device-iris.htm#device	No noted change from above requirements.	Please submit 1 electronic copy ONLY with electronic signatures where possible in PDF format to ethics@austin.org.au(with the relevant report completed)	No noted change from above requirements.	No noted change from above requirements.	No noted change from above requirements.

Item Type	Non-SERP Study (Local HREC Requirements)	SERP Study (Local RGO Requirements)	Alfred Hospital Ethics Committee	Austin Health HREC	Melbourne Health HREC	Peter MacCallum Cancer Centre Ethics Committee	St Vincent's Hospital (Melbourne) HREC D
INDIVIDUAL SUSARs The provision of individual SUSARs may vary between sponsors. They are not always supplied to clinical trial sites.	Do not report to HREC If supplied by sponsor file on site (Unless the sponsor or PI/SUB feels the event necessitates immediate reporting.)	Do not report to RGO If supplied by sponsor file on site (Unless the sponsor or PI/SUB feels the event necessitates immediate reporting.)	-	Please submit 1 electronic copy ONLY with electronic signatures where possible in PDF format to ethics@austin.org.au (with the relevant report completed) If from Victoria, these are reported to VMIA	-	Individual AE or SAE and individual SUSAR or USADE events that have occurred at a site that is required to report to the Peter Mac Ethics Committee as the reviewing HREC must be submitted only if the information materially impacts on the continued ethical acceptability of the trial or requires or indicates the need for a change to the trial protocol, including changed safety monitoring in the view of the investigator or sponsor.	-
LINE LISTINGS 3-6mthly	Submit in intervals as received from the sponsor. Include sponsor and investigator comments as to whether action is planned for the trial on the basis of the reports.	Submit in intervals as received from the sponsor. Include sponsor and investigator comments as to whether action is planned for the trial on the basis of the reports.	These should be (a) reviewed by the PI, (b) acknowledged to the sponsor, (c) reported to the HREC (with a comment from the PI) ONLY IF the listing reveals significant information. The Alfred Hospital Ethics Committee does not wish to receive any listings (such as quarterly or other line listings) from sponsors unless the listing has been assessed by the Principal Investigator as containing significant safety information that should be drawn to the attention of the Ethics Committee. In this instance, the listing should be sent to the Alfred Health Ethics And Research Governance Office and accompanied by a comment from the Principal Investigator on the significance of the information, the possible impact on study participants and action taken or recommended.	Please submit 1 electronic copy ONLY with electronic signatures where possible in PDF format to ethics@austin.org.au (with the relevant report completed) Submission IS NOT required when Austin Health is a participating site http://www.austin.org.au/RE/SafetyReporting	-	At least six monthly: SUSAR/USADE Line Listing/Summary Report. All submissions MUST complete the SUSAR/USADE Line Listing Report form.	St Vincent's Hospital HREC requires the submission of: A six monthly line listing of all SUSARs (both Australian and International) including sponsor and investigator comment as to whether action is planned for the trial on the basis of the reports (EU format is acceptable)

Item Type	Non-SERP Study (Local HREC Requirements)	SERP Study (Local RGO Requirements)	Alfred Hospital Ethics Committee	Austin Health HREC	Melbourne Health HREC	Peter MacCallum Cancer Centre Ethics Committee	St Vincent's Hospital (Melbourne) HREC D
ANNUAL SAFETY REPORTS An EU Annual Safety Report (ASR) (or similar format report)	For each report include sponsor and investigator comment as to whether action is planned for the trial on the basis of the reports.	For each report include sponsor and investigator comment as to whether action is planned for the trial on the basis of the reports.	These need to be reported to HREC promptly with a comment by the PI stating the implications of the findings on the trial.	Please submit 1 electronic copy ONLY with electronic signatures where possible in PDF format to ethics@austin.org.au (with the relevant report completed)	-	At least annually: Annual Safety Report. All submissions MUST complete the SUSAR/USADE Line Listing Report form.	
IB/PRODUCT INFORMATION (Whichever applies)	Please submit to the HREC using a cover sheet signed by the PI/SUB advising whether or not the changes may have an impact, including :· Full revised IBSummary of changes (if not included in the revised IB)	If there is local impact, advise the RGO.IB updates/updates to Product Information are directed to the HREC then the RGO	Updated IBs (if not part of an amendment) should be forwarded to the Alfred Health Ethics and Research Governance Office on receipt from the sponsor, with the following core documents:1. Full revised IB and a summary of changes (if not included in the revised IB)2. An Impact Statement signed by the Principal Investigator (advising whether, or not, the changes may have an impact on study participants).	Please submit 1 electronic copy ONLY to ethics@austin.org.auThis can be found here: http://www.austin.org.au/RE/ActiveProjects/#Section1	-	At least annually: Investigator Brochure or Product Information update. All submissions MUST complete the SUSAR/USADE Line Listing Report form.	St Vincent's Hospital HREC requires the submission of:An annual update of the investigators brochure, or product information (for products which are approved in Australia, or where an IB is no longer maintained)
PROTOCOL VIOLATIONS / DEVIATIONS	Report to the HREC ONLY if in the opinion of the PI/SUB it impacts on the research and action is planned, or there are ethical implications. Use the appropriate proforma., include advice from PI/SUB on nature of BH impact	Report to the RGO ONLY if in the opinion of the PI/SUB it impacts on the research and action is planned, or there are ethical implications. Use appropriate proforma., include advice from PI/SUB on nature of impact on BH	Researchers should provide written details to the Ethics Committee of protocol violations or deviations when: There are safety or ethical implications for the participant(s) The scientific integrity of the study is affected (normally the sponsor will advise this) The protocol methodology causes the protocol deviation/violation to occur (eg. exclusion criteria too strict) The conduct of the study causes the protocol deviation/violation to occur (eg. rotating staff not detailing consent procedures in patient notes). An acknowledgement receipt will be sent by return email.	Please submit 1 electronic copy with electronic signatures to ethics@austin.org.au This can be found here: http://www.austin.org.au/RE/ActiveProjects/#Section2	-	-	Minor protocol deviations which do not carry significant ethical / administrative implications or consequences do not need to be reported to the HREC. However, all such deviations must be recorded in the study file and reported to the sponsor. Major deviations and protocol violations which pose a risk to patient safety, or have ethical or significant administrative implications must be reported to the HREC and the Sponsor soon as possible. Major deviations/violations must be reported by completing and submitting a single copy of the following form and maybe submitted to the Research Governance Unit via email, fax or hard copy.

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GENERAL NOTES	DoH Forms to be used. Select the appropriate template and email the completed form to HREC@BarwonHealth.org.au	DoH Forms to be used. Select the appropriate template and email the completed form to RG0@BarwonHealth.org.au	DoH Forms to be used. Select the appropriate template and email the completed form to research@alfred.org.au	DoH Forms can be used. Select the appropriate template and 1 electronic copy ONLY with electronic signatures where possible in PDF format to ethics@austin.org.au Please note all supporting electronic documents must be labelled according to the Naming Requirement for Electronic Files using the approved acronyms and document types• For immediate confirmation that your email has reached us, set up an automated 'Delivery Receipt Notification' before you send your email. • Please title the subject of the email xxxx	DoH Forms to be used.	DoH Forms to be used.	All documents should be submitted electronically to research.ethics@svhm.org.au and be accompanied with the template Cover Sheet and Fee Form. Hard copy submission is also required.

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