NHMRC AUSTRALIAN HEALTH ETHICS COMMITTEE (AHEC) POSITION STATEMENT

Monitoring and reporting of safety for clinical trials involving therapeutic products

MAY 2009

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1. Purpose and scope

This Position Statement replaces the AHEC HREC Alert No.1, 18 April 2007.

The National Statement on Ethical Conduct in Human Research[1] *(National Statement)* recognises that sponsors, investigators/researchers*, institutions and HRECs all have relevant responsibilities.

This Position Statement is designed to clarify the responsibilities of all parties in relation to reports of adverse events (AEs), including serious adverse events (SAEs) and suspected unexpected serious adverse reactions (SUSARs), occurring in clinical trials for which institutions are responsible and that Human Research Ethics Committees (HRECs) have reviewed and given ethical approval.

Investigators must submit progress reports of the trial status to the IRB/IEC.[1,2] This Position Statement specifies ***minimum requirements*** **regarding safety reporting** in order to comply with the National Statement, in particular Sections 3.3.19 – 3.3.22 *Monitoring of approved clinical trials* and Section 5.5 *Monitoring approved research*. Depending on the complexity, design and risk perceived, an institution and/or the HREC responsible for the trial may require that additional information be reported. However, as far as possible, a uniform approach across trials in Australia is desirable so that investigators and sponsors are able to meet these obligations.

Terms used within this document are as defined in references 1-6. Other adverse health outcomes relating to medical practice occurring in health care institutions (and that are unrelated to a clinical trial) are outside the scope of this document. This Position Statement is not intended to affect institutional safety reporting procedures that may be required for other purposes (eg insurance arrangements).

The content of European Union (EU) Annual Safety Reports (ASR) and SUSAR line listings are described in reference 7.

2. Investigator/researcher responsibilities

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

The investigator/researcher must report all SAEs to the sponsor immediately (within 24 hours) in accordance with the study protocol and GCP guidelines as adopted by the TGA.[2]

If the investigator/researcher is also the study sponsor, see section 5 and 6 for additional responsibilities.

* The term 'investigator' is used here, consistent with Reference 2. The term 'researcher' is synonymous with 'investigator' for the purposes of this Position Statement.

For each trial, investigator/researcher must also provide:

2.1	In accordance with individual institutional requirements *NB: institutions should seek to keep individual requirements to minimum or utilise such requirements in a highly targeted manner if these are particular safety concerns*	• to institution (or HREC as specified by institution) – AEs or SAEs occurring at their site(s)
2.2	In a prompt manner	• to HREC responsible for trial – information which materially impacts the continued ethical acceptability of the trial or – information that requires, or indicates the need for, a change to the trial protocol, including changed safety monitoring in the view of the investigator or sponsor.
2.3	At least six-monthly	• to HREC responsible for trial – listing of all SUSARs, Australian and international, occurring with a compound – including sponsor and investigator comment as to whether action is planned for the trial on the basis of the reports – EU format is acceptable.
2.4	At least annually	• to HREC responsible for trial – an updated Investigator Brochure, or – an EU ASR (or similar format report), or – current, approved Product Information (PI), if appropriate (eg in a study for a product approved in Australia or where an Investigator Brochure is no longer maintained) – other reports consistent with section 5.5.5 of the *National Statement*[1] and *Good Clinical Practice (GCP)* as adopted by the *Therapeutic Goods Administration (TGA)*.[2]

Regarding annual reports:

- for each, include sponsor and investigator comment as to whether action is planned for the trial on the basis of the reports
- for trials that are investigator or collaborative group sponsored in which an IB, EU ASR or PI are not available, then a trial update may be submitted that provides appropriate review of safety information in the previous 12 months
- when sponsors need to provide some or all of this information to the investigator, sponsors need to include clear advice as to whether the information requires or indicates the need for a change in the trial protocol including changed safety monitoring
- to enable investigators to fulfill their responsibilities to institutions, sponsors need to respond to requests from investigators for clarification of such advice or information
- when investigators report this information to the institution they should provide their own opinion in regard to potential impact on ethical acceptability and need for action
- the timing of ASR production by sponsors and the progress report to the ethics committee by an investigator may be asynchronous.

3. Institutional responsibilities

The *National Statement*[1] describes the ultimate responsibilities of institutions for monitoring the conduct of approved research in section 5.5 *Monitoring approved research* and describes specific responsibilities for clinical research in sections 3.3.19 – 3.3.22 *Monitoring of approved clinical research*.

Institutions in Australia have a wide variety of models of fulfilling research governance and ethical review responsibilities. Institutions and HRECs should work together to establish that an adequate mechanism is in place to monitor the conduct of clinical trials at sites for which they have responsibility. Some mechanisms are described in section 5.5 of the *National Statement*.[1]

4. HREC responsibilities

HRECs have an obligation to ensure that any changes in the benefit/risk balance of a study are compatible with continued ethical approval.

To support the requirements outlined in sections 3.3.19 – 3.3.22 and 5.5 of the *National Statement*[1], HRECs:

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

This may lead to the following mechanisms during the conduct of the study:

A. Use the monitoring arrangements described in the trial protocol by the sponsor. These could include one or more of the following:
   - a pharmacovigilance group in a company-sponsored clinical trial
   - a trial management committee
   - a data safety monitoring board
   - a simpler but separate review process for investigator or collaborative sponsored trials.

B. Conduct review of safety information within the HREC if the HREC has sufficient resources and expertise.

5. Sponsor responsibilities

Sponsors have a significant role in supporting investigators/researchers in meeting their obligations for safety reporting to institutions.

In a prompt manner, sponsors must communicate to investigators information which could adversely affect the safety of subjects, materially impact the continued ethical acceptability of the trial or that requires (or indicates the need for) a change to the trial protocol, including changed safety monitoring[2].

Sponsors should:

- establish safety monitoring processes that are commensurate with the risk, size and complexity of the proposed research
- be in regular communication with the investigators
- keep investigators up to-date with safety issues in a trial in a manner that is consistent with the risk, size and complexity of the proposed research
- provide to investigators the periodic information listed under section 2 to facilitate investigator submission to the relevant HREC.

ONLY IF the investigator, HREC or sponsor consider it to be necessary because of the risk, size or complexity of the proposed research, is the sponsor required routinely to send individual SUSARs from Australian or international sites to investigators.

6. Reporting to the TGA

Sponsors are responsible for reporting individual case safety reports (ICSR) to the TGA in accordance with expedited reporting guidelines.[3]

In investigator or collaborative group sponsored studies, responsibility for reporting adverse reactions to the TGA rests with the investigator or collaborative group.[4]

7. References

1. The *National Statement on Ethical Conduct in Human Research* (NHMRC 2007) (*National Statement*). (http://www.nhmrc.gov.au/publications/synopses/e72syn.htm)
2. Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95) - annotated with TGA comments. DSEB. July 2000. (http://www.tga.gov.au/docs/html/ich13595.htm)
3. Note for Guidance on Clinical Safety Data Management: Definitions and Standards for Expedited Reporting (CPMP/ICH/377/95). Annotated with TGA comments, August 2001. (http://www.tga.gov.au/docs/html/ich37795.htm)
4. Australian Guideline for Pharmacovigilance Responsibilities of Sponsors of Registered Medicines Regulated by Drug Safety and Evaluation Branch. Australian Government Department of Health and Ageing. Therapeutic Goods Administration. July 2003, amended 31 May 2005. (http://www.tga.gov.au/adr/pharmaco.htm)
5. Access to Unapproved Therapeutic Goods – clinical trials in Australia. Australian Government Department of Health and Ageing. Therapeutic Goods Administration. Oct 2004. (http://www.tga.gov.au/docs/html/clintrials.htm)
6. Human Research Ethics Committees and the Therapeutic Goods Legislation. Commonwealth Department of Health and Aged Care. Therapeutic Goods Administration. June 2001. (http://www.tga.gov.au/docs/html/hrec.htm)
7. Detailed guidance on the collection, verification and presentation of adverse reaction reports arising from clinical trials on medicinal products for human use. ENTR/CT3, Revision 2, April 2006, European Commission. (http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/vol-10/21_susar_rev2_2006_04_11.pdf)