# SAFETY REPORTING FOR CLINICAL TRIALS

## PROCEDURE©

## DOCUMENT SUMMARY/KEY POINTS

- This document outlines procedures for safety reporting in clinical trials, to ensure compliance with current Australian legislation and Good Clinical Practice as described in the TGA Note for Guidance on Good Clinical Practice CPMP/ICH/135/95 1 and the NHMRC National Statement on Ethical Conduct in Human Research.
- This policy reflects:
  - the intentions of the AHEC 2009 Statement to minimise documentation relating to safety reporting.
  - NSW Health policy relating to HRECs and RGOs
  - TGA requirements for drug and medical device safety reporting
  - Good clinical practice (GCP) guidelines for safety reporting

## CHANGE SUMMARY

- Sections 1 and 2 are new.
- Links updated

## READ ACKNOWLEDGEMENT

- This document should be referenced and adhered to by researchers conduction clinical trials across Sydney Children's Hospitals Network.

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# 1 Purpose and Scope

One of the main aims of Good Clinical Practice (GCP) is the safety and wellbeing of clinical study participants. It is important to collect information on the potential adverse effects of new drugs/devices and there are strict guidelines for reporting these to all researchers working on the study as well as the relevant ethics committees and regulatory authorities.

In addition, the Sponsor is responsible for the ongoing review of the safety profile of a drug/device and for making any required updates to the information contained within the Investigator Brochure/Product Information. If SCHN is acting as the Sponsor, any update to the Investigator Brochure/Product Information remains the responsibility of the drug/device manufacturer. The Sponsor must also ensure that participants are made aware of these changes.

Drug/device manufacturers may also require the collection of specific adverse event information, or the use of a particular process for following adverse events. In these instances, the Study Team should incorporate these requirements while still adhering to this Procedure.

# 2 Policy / Regulation References

The following websites and references address the requirements for this Procedure.

***Australian:***

- National Statement on Ethical Conduct in Human Research 2007 (updated May 2015)
- Therapeutic Goods Administration (TGA):
  - Access to Unapproved Therapeutic Goods - Clinical Trials in Australia (October 2004)
  - Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95, July 2000)
  - Note for Guidance on Clinical Safety Data Management: Definitions and Standards for Expedited Reporting (CPMP/ICH/377/95, July 2000)
  - Australian requirements and recommendations for pharmacovigilance responsibilities of sponsors of medicines
  - The Advisory Committee on the Safety of Medicines (ACSOM)

***International:***

- International Conference on Harmonisation (ICH):
  - ICH Guideline for Good Clinical Practice (E6(R1), June 1996)
  - ICH Clinical Safety Management: Definitions and Standards for Expedited Reporting (E2A, October 1994)

# 3 Commonly Used Acronyms

| Abbreviation | |
|---|---|
| **ADEC** | Adverse Drug Evaluation Committee |
| **ADE** | Adverse Device Event |
| **ADR** | Adverse Drug Reaction |
| **ADRAC** | Adverse Drug Reaction Advisory Committee |
| **ADRU** | Adverse Drug Reaction Unit |
| **AE** | Adverse Event |
| **AHEC** | Australian Health Ethics Committee |
| **ARCS** | Non-profit Professional Development Association for the Therapeutics Industry |
| **ASR** | Annual Safety Report |
| **CIOMS** | Council for International Organizations of Medical Sciences |
| **CRF** | Case Report Form |
| **CRO** | Contract Research Organisation |
| **CTN** | Clinical Trial Notification (Scheme) |
| **CTX** | Clinical Trial Exemption (Scheme) |
| **DSMB** | Data Safety Monitoring Board |
| **EU** | European Union |
| **FDA** | USA Food and Drug Administration |
| **GCP** | Good Clinical Practice[1] |
| **HREC** | Human Research Ethics Committee |
| **IIMS** | NSW Health's electronic Incident Information Management System |
| **IRB** | Institutional Review Board |
| **NHMRC** | National Health and Medical Research Council |
| **RGO** | Research Governance Officer |
| **SAE** | Serious Adverse Event |
| **SOP** | Standard Operating Procedure |
| **SUADE** | Serious Unanticipated Adverse Device Event |
| **SUSAR** | Serious Unexpected Suspected Adverse Reaction |
| **TGA** | Therapeutic Goods Administration |
| **WHO** | World Health Organisation |

# 4 Definitions

## 4.1 Definitions (General)

### *4.1.1 Co-ordinating Investigator (CI)*

The individual who takes overall responsibility for the research project and submits the project for ethical and scientific review. They are responsible for ongoing communication with the HREC and passing on any outcomes from this to the Principal Investigators. For single centre research, Co-ordinating Investigator and Principal Investigator are synonymous.[2]

### *4.1.2 Clinical Trial Notification (CTN) (Scheme)*

There are two schemes under which clinical trials involving therapeutic goods may be conducted, the CTX Scheme and the CTN Scheme. It is the decision of the Sponsor and HREC as to which scheme is used. As a general rule, phase III, IV and bioavailability/ bioequivalence studies of medicines are most suited to the CTN scheme. However, the CTN Scheme can also be an option for earlier phase (I & II) studies if there is adequate preclinical review available, especially on safety. The CTN form is used to notify the TGA of HREC and institutional approval to start a trial being conducted under the CTN Scheme at a site[3].

### *4.1.3 Clinical Trial Exemption (CTX) (Scheme)*

Clinical trials are conducted under CTX Scheme when the CTN Scheme is not suitable. A Sponsor cannot commence a CTX trial until written advice and approval has been received from the TGA regarding the application; and approval for the conduct of the trial has been obtained from a HREC and the institution at which the trial will be conducted[3].

### *4.1.4 Principal Investigator (PI)*

The individual who takes responsibility for the overall conduct, management, monitoring and reporting of research conducted at a site, and submits the research project for site authorisation.[2]

### *4.1.5 Reviewing HREC*

The HREC which undertook the ethical and scientific review and provided approval for the research project.[2]

### *4.1.6 Sponsor*

An individual, company, institution, or organisation which takes responsibility for the initiation, management, and/or financing of a clinical trial.[1] A sponsor must be an “Australian Entity” for the purposes of the CTN or CTX Schemes[5].

### *4.1.7 Therapeutic Good*

A good which is represented in any way to be, or is likely to be taken to be, for therapeutic use. Therapeutic use means use in or in connection with:

- Preventing, diagnosing, curing or alleviating a disease, ailment, defect or injury;
- Influencing inhibiting or modifying a physiological process;

- Testing the susceptibility of persons to a disease or ailment;
- Influencing, controlling or preventing conception;
- Testing for pregnancy; or
- Replacement or modification of parts of the anatomy. [2]

### *4.1.8 (Trial) Site*

The location(s) where trial related activities are actually conducted[1].

## 4.2 Definitions (Drugs)

### *4.2.1 AE (Drug)*

Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An adverse event can therefore be any unfavourable and unintended sign, symptom, or disease temporally associated with the use of a medicinal (investigational /experimental) product, whether or not related to this product[4].

### *4.2.2 Adverse Drug Reactions - ADRs*

For unapproved medicinal products (i.e. investigational drug in clinical trials or approved drugs used at doses or in ways that are not approved), all noxious and unintended responses to a medicinal product related to any dose should be considered adverse drug reactions[4].

The phrase “responses to a medicinal product” means that a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility, i.e. the relationship cannot be ruled out[4].

For marketed medical products the well-accepted definition of an adverse drug reaction in the post-marketing setting is: a response to a drug which is noxious and unintended and which occurs at doses normally used in humans for prophylaxis, diagnosis or therapy of diseases or for modification of physiological function[4].

### *4.2.3 Unexpected ADR*

An adverse reaction, the nature or severity of which is not consistent with the applicable scientific information (e.g. Investigator’s Brochure for an unapproved investigational product or Product Information document or similar for an approved, marketed product)[1].

Adverse reactions which currently appear in the Australian Product Information and/or Investigator’s Brochure but are described as having no established causal relationship should be considered unexpected for the purposes of reporting to the TGA. If a previously unexpected adverse reaction is added to the Australian Investigator’s Brochure, then that particular reaction ceases to be unexpected in Australia.[4]

### *4.2.4 Serious Adverse Events - SAEs*

A serious adverse event (experience) or reaction is any untoward medical occurrence that at any dose:

- Results in death,
- Is life-threatening, (an event/reaction in which the patient was at risk of death at the time of the event/reaction, not an event/reaction which hypothetically might have caused death if it were more severe.)
- Requires inpatient hospitalisation or prolongation of existing hospitalisation,
- Results in persistent or significant disability/incapacity,
- Is a congenital anomaly/birth defect[4];

Medical and scientific judgement should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalisation but may jeopardise the patient or may require intervention to prevent one of the other outcomes listed in the definition above. These should also usually be considered serious.

Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood duscrasias or convulsions that do not result in hospitalisation; or development of drug dependency or drug abuse[4].

### *4.2.5 Serious Unexpected Suspected Adverse Reactions - SUSARs*

These are serious adverse events for which there is some degree of probability that the event is related to the investigational product, and unexpected[4]. The causality assessment may be made after the data is un-blinded (by the Data Safety Monitoring Board - DSMB).

**Note:** Serious and Severe are not synonymous.

> **Severity** usually refers to the intensity of an event (e.g. mild, moderate or severe). The event itself however may be of relatively minor medical significance (such as a severe headache).
>
> **Seriousness** is based on a patient/event outcome or action criteria usually associated with events that pose a threat to a patient's life or functioning. Seriousness, not severity, forms the basis of regulatory reporting obligations. [4]

## 4.3 Definitions (Medical Devices)

### *4.3.1 AE (Device)*

Any undesirable clinical occurrence in a subject whether it is considered to be device related or not, that includes a clinical sign, symptom or condition and/or an observation of an unintended technical performance or performance outcome of the device[3].

### *4.3.2 Adverse Device Event ADE*

A clinical sign, symptom or condition that is causally related to the device implantation procedure, the presence of the device, or the performance of the device system[3].

### *4.3.3 Serious Adverse Events - SAE (device)*

Any adverse medical occurrence that:

- Led to a death;

- Led to a serious deterioration in health of a patient user or other. This would include:
  - A life threatening illness or injury;
  - A permanent impairment of body function or permanent damage to a body structure;
  - A condition requiring hospitalisation of increase length of existing hospitalisation;
  - A condition requiring unnecessary medical or surgical intervention; or
  - Foetal distress, foetal death or a congenital abnormality/birth defect;
- Might have led to death or a serious deterioration in health had a suitable action or intervention not taken place. This include:
  - A malfunction of a device such that it has to be modified or temporarily/permanently taken out of service; or
  - A factor (a deterioration in characteristics or performance) found on examination of the device)[3].

### *4.3.4 Serious ADE*

A device related serious adverse event[3].

### *4.3.5 Unanticipated ADE*

Any undesirable clinical occurrence in a subject considered to be device related and not listed in the device technical manuals (or not listed in the appropriate section on the Adverse Event case report form).[3]

# 5 Bodies Relevant to Safety Reporting

It is the responsibility of the Sponsor and investigators to make sure that they are aware of the current local, national and international responsibilities for safety reporting in clinical trials.

The following entities provide guidance/have responsibility with respect to monitoring the safety of clinical trials in Australia:

## 5.1 National Health and Medical Research Council (NHMRC)

The "National Statement on Ethical Conduct in Human Research" (The National Statement)[6] sets standards for the ethical conduct by any individual, institution or organisation of human research in Australia. It outlines the expectations for investigators, institutions and HRECs to monitor safety.

## 5.2 HREC & RGO Requirements

The National Statement requires approving HRECs to be informed as soon as possible of any new safety information that may impact on the ethical acceptability of the trial, or the need for trial amendments.

SCHN has a responsibility for ensuring that there are mechanisms in place for reporting and reviewing SAEs, serious ADRs, SUSARs and serious adverse device events at each site for which it is responsible.

The SCHN HREC and RGO abide by NSW Health policies and guidance[2,7-10]. The reporting requirements for SCHN HREC and RGO are summarised in the Appendix.

## 5.3 TGA

The TGA is the federal authority responsible for monitoring the safety of therapeutic goods used in Australia, including those under development in clinical trials. The TGA has adopted (with annotation) the European "Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95)"[1] and "*Note for Guidance on Clinical Safety Data Management: Definitions and Standards for Expedited Reporting (CPMP/ICH/377/95)*"[4].

Additional guidance on the TGA's requirements for management and reporting of adverse events can be found in: "*Access to Unapproved Therapeutic Goods – Clinical Trials in Australia – October 2004*"[3] and "*The Australian Clinical Trial Handbook (March 2006)*"[5].

The safety reporting requirements of the TGA are summarised in section 6.2.2 and the Appendix.

## 5.4 International Regulatory Bodies

If a clinical trial is sponsored by a foreign organisation, or conducted in a country/ies outside Australia, then expedited reporting to the regulatory authority of those country/ies may be required. Trial sponsors should agree in advance who will be responsible for safety reporting to foreign agencies, as well as the TGA, HRECs and Governance offices (as appropriate).

The U.S. Department of Health and Human Services Office for Human Research Protections publishes an updated list of International Human Research Standards that may be helpful in assessing international regulatory requirements[11]. Investigators should seek advice if unsure what safety reporting is required, and what safety reporting they are responsible for.

## 5.5 Public Health Organisations

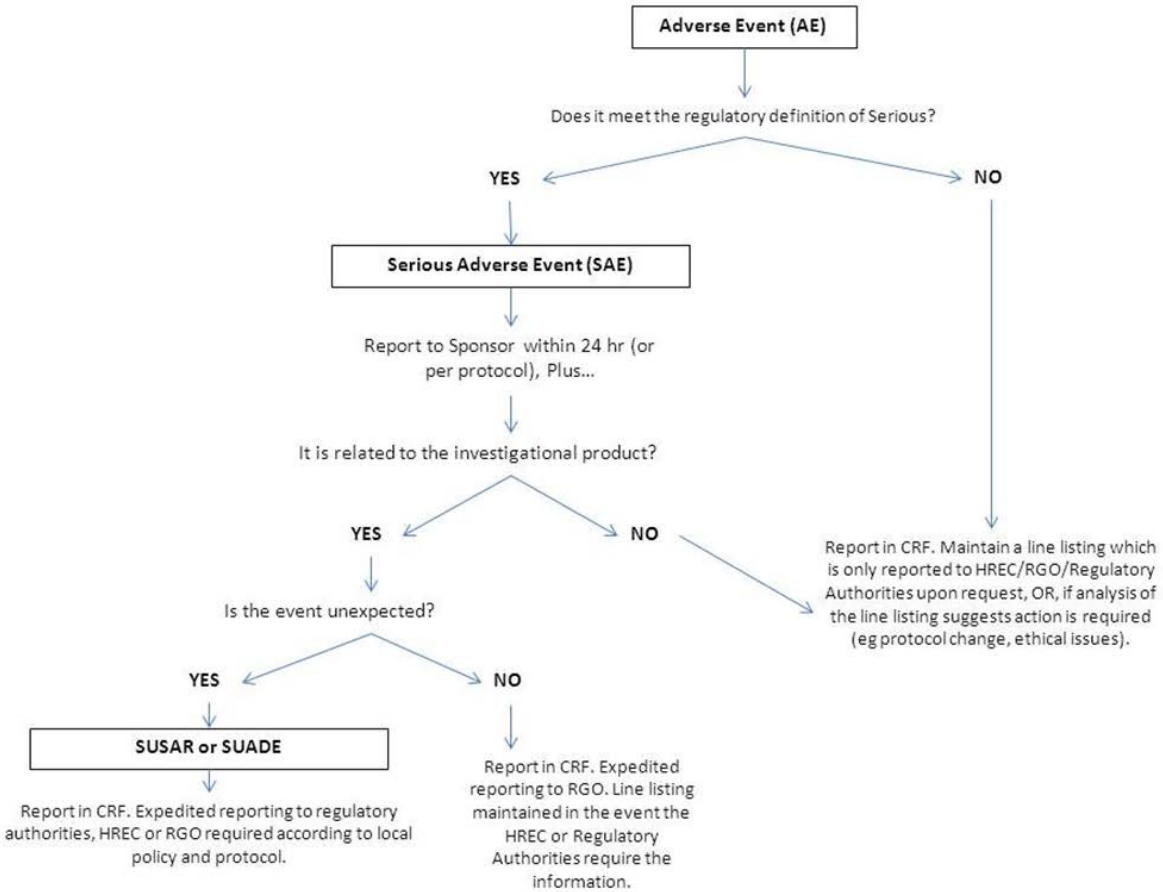
Where an event has occurred at a site within NSW Health, the incident is also reportable under the clinical governance policy of the Public Health Organisation, including the incident management process outlined under Policy Directive PD2014_004 Incident Management Policy[10].

If a serious adverse event is a "Reportable Incident" it requires a root cause analysis in accordance with Division 6C of the Health Administration Act 1982 (NSW). This requirement is additional to any reporting required to the reviewing HREC, RGO, the TGA or international regulatory bodies.

# 6 Reporting safety information

It is the responsibility of the investigator/researcher to capture and report all AEs identified in the protocol, including SAEs and SUSARs, which occur at their site1. When SCHN is sponsor for a trial, the investigator must comply with regulatory reporting requirements. A summary guide to the hierarchy of adverse events and reporting requirements is in Figure 1:

**Figure 1: Adverse Event Reporting Decision Tree**



All types of adverse events should be **categorised and graded** (for example, for severity or toxicity) according to the protocol or a standard international grading system as nominated in the protocol.

The **expectedness and causality** should be initially determined by the investigator but may subsequently be reviewed by the Sponsor, the Data Safety Monitoring Board or the Study Committee as indicated in the protocol.

- **Expectedness** refers to whether the adverse event was a known toxicity or adverse reaction. Expected events should be clearly listed in the protocol and parent/participant information sheets.

  The following documents/circumstances will be used to determine whether an adverse event/reaction is expected[4]:

  - For an unapproved medicinal product, the Investigator's Brochure will serve as the source document.
  - Reports, which add significant information on specificity or severity of a known, already documented serious ADR, constitute unexpected events. For example, an event more specific or more severe than described in the Investigator's Brochure would be considered "unexpected". Specific examples would be **(a)** acute renal failure as a labelled ADR with a subsequent new report of interstitial nephritis, and **(b)** hepatitis with a first report of fulminant hepatitis.
- Causality refers to the likelihood that the adverse event was caused by the experimental intervention/drug/device. A summary of what should be reported to whom and when for drug/device AEs, SAEs and SUSARs and other safety information is provided in the Appendix and section 6.2.2.

The next section provides the detailed reporting requirements for each category of safety information. A summary of what should what should be reported by whom, to whom, and the documentation and timeline requirements for trials being conducted at an SCHN site can be found in the Appendix.

## 6.1 AEs and Adverse Device Events (ADEs)

### *6.1.1 Time-frames for Reporting AEs, ADEs*

- Reporting of AEs and ADEs to the Sponsor is in accordance with the study protocol.
- AEs will be reported to the local HREC or Institutional Authority only when requested or according to institutional or HREC requirements. The NHMRC has stipulated that reporting of AEs to HRECs or institutions should be kept to a minimum and only utilised in a highly targeted manner if there are particular safety concerns[12].
- Reporting of AEs and ADEs to the TGA is only upon request.

### *6.1.2 Documentation Required for AEs, ADEs*

Documents that should be maintained as a record of AEs occurring during the clinical trial include:

- Source Documents i.e. a comprehensive medical record;
- Case Report Forms, where all adverse events are recorded.

The AEs that are targeted for reporting in case report forms should be clearly described in the protocol.

### *6.1.3 Responsibility for Reporting AEs, ADEs*

The Principal Investigator at each site is responsible for capturing and reporting all AEs occurring at their site in accordance with the study protocol, HREC, RGO and regulatory requirements.

## 6.2 SAEs (Drug and Device), SUSARs and SUADEs

### *6.2.1 Responsibilities and Time-frames for Reporting SAEs, SUSARs, and SUADEs*

All SAEs must be reported to the Sponsor immediately (usually within 24 hours) in accordance with the protocol and GCP[1,5].

Principal investigators of SCHN sites are responsible for expedited reporting of SUSARs/SUADEs that occur at their site to the approving HREC and SCHN RGO as applicable. Expected suspected SAEs that occur at a SCHN site should be reported as soon as possible to the SCHN RGO.

Where SCHN HREC is the approving HREC, an individual summary adverse event reporting form should be submitted within 24-72hours. This form can be found in the Research ethics intranet site (http://intranet.schn.health.nsw.gov.au/research/human-research-ethics). A copy of the information submitted to the HREC and their acknowledgement must be provided to the SCHN RGO (and in the case of multi-centre projects, to the coordinating investigator).

**For multi-centre research projects:**

All Sponsors must report **in a prompt manner** to investigators/ researchers any 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[1, 12]. Coordinating investigators are responsible for expedited reporting of this information to the approving HREC using the HREC's required forms. (For SCHN HREC, this information should be reported within 24-72hours). Principal investigators of SCHN sites should submit a copy of this information and HREC acknowledgement to the SCHN RGO.

At least six monthly, a listing of all SUSARs, Australian and International occurring with a compound, including investigator and sponsor comment as to whether action is planned for the trial on the basis of the reports, needs to be submitted to the approving HREC[12]. (For SCHN HREC, the EU format is acceptable or a summary of the six monthly SUSAR and SAE listings (Australian and International Events) on the form available on the Research ethics intranet site (http://intranet.schn.health.nsw.gov.au/research/human-research-ethics).

Depending on the complexity, design and risk perceived, the reviewing HREC and/or the Public Health Organisation has the discretion to require that additional information be reported for adverse events.

Sponsors are responsible for appropriate safety reporting to regulatory agencies, such as the TGA (see 6.2.2).

### *6.2.2 TGA reporting requirements and forms*

In Australia, the TGA requires[3,4]:

- Rapid reporting of individual SUSARs and SUADEs within 7 calendar days for:
  - Fatal and unexpected events occurring within Australia;
  - Life-threatening and unexpected events occurring within Australia.

  This can be an initial report with a full report following within 8 days.
- Reporting within 15 calendar days for:
  - All other individual SUSARs and SUADEs that are not fatal or life-threatening occurring within Australia.
- Sponsors are expected to continually monitor safety of clinical development programs and advise the TGA **within 72 hours** about:
  - Significant issues arising from the analysis of overseas reports
  - Action which has been taken by another country's regulatory agency

International SUSARs are preferably amalgamated into a single report.

The minimum criteria that must be provided in expedited safety reports to regulatory authorities are:

- An identifiable patient;
- A suspect medicinal product/device;
- An identifiable reporting source;
- An event or outcome that can be identified as serious and unexpected, and for which there is a reasonable suspected causal relationship.3

The full list of desirable elements to include in an expedited safety report is outlined in Appendix 2 of Reference 4.

Sponsors are encouraged to submit expedited reports with any available details on the understanding that further information is being sought and will be submitted in due course. Also, in relation to CTN schemes, it is preferable to accompany a report with appropriate information (such as an Investigator's Brochure and/or protocol) or interpretation, given the TGA will not have reviewed any safety (or other) data concerning the trial.

For a purely post-marketing study with drug used within marketing approval, ADRs are to be reported directly to Adverse Drug Reaction Unit (ADRU) using the ADRAC form available at: http://www.tga.gov.au/safety/problem-medicines-forms-bluecard.htm or reported electronically (see http://www.tga.gov.au/safety/problem.htm)

Clinical trial SUSARs may be submitted using the "Blue Card" system or using an appropriate format which contains the same information (e.g. CIOMS form). The "Blue Card" may be downloaded from the TGA website using the following link: http://www.tga.gov.au/safety/problem-medicines-forms-bluecard.htm

While this information may be submitted to the Office of Product Review, it is preferable to submit SUSARs directly to the Experimental Products Section as per the details below.

| | |
|---|---|
| **Email** | eds@tga.gov.au |
| **Fax** | +61 2 6232 8112 |
| **Postal address** | The Medical Officer<br>Experimental Products Section<br>Office of Scientific Evaluation<br>Therapeutic Goods Administration<br>PO Box 100<br>Woden ACT 2606<br>Australia |

Clinical trial SUADEs should be submitted using the "Medical Device Incident Report" form which may be downloaded from the TGA website using the following link: http://www.tga.gov.au/safety/problem-device-report-industry.htm .

SUADEs may be forwarded to the following address.

The Medical Officer
Office of Device Authorisation
Therapeutic Goods Administration
PO Box 100
Woden ACT 2606

### *6.2.3 Documentation for Reporting SAEs, SUSARs, and SUADEs*

Documents that may be required for capturing and reporting SAEs and SUSARs include the following:

- Source Documents i.e. a comprehensive medical record. Maintaining the primary record that evidences SAEs or SUSARs is a mandatory requirement;
- Case report forms that collect all SAEs and SUSARs as specified in the protocol;
- Sponsor specific SAE/SUSAR collection tools;
- Regulatory authority specific reporting forms, such as CIOMS form (international) or ADRAC form/Medical Devices Incident Form (TGA);
- HREC correspondence regarding individual or summary adverse event reporting forms.

## 6.3 Urgent Safety Related issues

Where it is necessary to eliminate an immediate hazard to research participants, modifications or changes to the research project will be implemented without prior HREC review and site authorisation.

The CI/Site PI will notify the approving HREC and RGO of amendments arising from urgent safety-related events immediately and in writing (email is acceptable). The CI will submit the implemented modification or change, the reasons for it, and, if appropriate, the proposed protocol amendment(s) to the HREC for review within 5 working days and the Principal Investigator will advise the Research Governance Officer of developments[9].

Reports of urgent safety-related measures are in addition to adverse event reporting requirements and are covered by row 1 in the Appendix.

## 6.4 Overdoses

Sponsors should report to the TGA serious and unexpected adverse reactions that occur as a result of cases of accidental or intentional overdose. This includes reports that indicate that the taking of the suspect drug led to suicidal ideation and a subsequent overdose of the suspected medicine or other medication. Reports of overdose with no associated adverse reactions should not be reported in an expedited fashion[3].

# 7 Emergency unblinding for an assessment of causality or participant treatment decisions

The trial protocol should explicitly state when unblinding can occur and how it will be handled[3].

Emergency unblinding should be a last resort and only undertaken if the information is going to impact the ongoing treatment of the participant or expedited reporting is required.

The Sponsor should ensure that the coding system will allow rapid identification of the product in case of a medical emergency[3].

If the code is broken prematurely or accidentally, the investigator must promptly document this and explain it to the Sponsor. The investigator should ensure that the randomisation code is broken only in accordance with the protocol.

Although best to maintain the blind for all patients prior to final study analysis, when expedited reporting is required, it is recommended that the sponsor break the blind for that specific patient, even if the investigator has not. When possible and appropriate, the blind should be maintained for persons, such as biometrics personnel, responsible for analysis and interpretation of results at the study's conclusion[4].

# 8 Annual Safety Reporting requirements

For each trial, an annual progress report and final report must be submitted at least annually to the approving HREC[5,12].

These reports should include:

- an updated Investigator Brochure (IB), or
- an EU Annual Safety Report (or similar format report), or
- current, approved Product Information, if appropriate (e.g. in a study for a product approved in Australia or where an Investigator Brochure is no longer maintained)
- for trials where an IB, EU ASR or product information is not available, then a trial update maybe submitted that provides appropriate review of safety information in the previous 12 months
- other reports consistent with section 5.5.5 of the *National Statement*[6] and GCP[1] as adopted by the TGA.

For each report the sponsor and investigator comment as to whether action is planned for the trial on the basis of the reports.

Annual and final reports are to be submitted using the template stipulated by the reviewing HREC. Reports for the SCHN HREC should be submitted on the form available on the Research ethics intranet site (http://intranet.schn.health.nsw.gov.au/research/human-research-ethics) in the Resources ➔ Human Ethics ➔ Adverse Events section.

**For single site clinical research projects**, the Coordinating Investigator is responsible for submitting the progress report to the approving HREC[7], and acknowledged copy to the SCHN RGO.

**For multi-site research projects**:

- The Co-ordinating Investigator collates the site reports and submits to the approving HREC as a single report[8]. HREC acknowledgement copy is then provided to Principal Investigator at SCHN for submission to SCHN RGO.

# 9 Review of Safety Reports by HRECs and Research Governance Managers

Upon receipt of a safety report the lead HREC will review the report and take the appropriate course of action which may include[2]:

- Acknowledging receipt of the report
- Noting of the event
- Referral to the lead HREC's scientific sub-committee/scientific expertise for advice
- Immediate request for additional information from the Coordinating Investigator or local Principal Investigator
- Other actions as recommended by the HREC
- Temporary hold or immediate discontinuation of ethical or site specific approval

Where the lead HREC considers it appropriate that the report requires the immediate suspension or discontinuation of the ethical approval of the research project, the lead HREC must immediately notify the Coordinating Investigator, local Principal Investigators and the Research Governance Offices at all other sites at which the project is being conducted. This must be followed by notice in writing, within 3 working days[2].

Upon receipt of a HREC Acknowledgment on safety report, the RGO will:

- Acknowledging receipt of the report
- Noting of the event
- Take actions as recommended by HREC
- In the case of patient death a copy of the HREC AE report will be forwarded by the SCHN RGM to the SCHN Patient Safety Officer in Clinical Governance.

Notification of the HREC or RGO response and recommendations, other than discontinuation, will be given to the submitting Investigator in writing within 10 days of the review meeting[2].

# 10 IIMS reporting

In the event a serious adverse event is identified as a clinical incident to be managed in accordance with PD2014_004 Incident Management[10], the IIMS report should clearly identify that the incident occurred within a clinical trial. The RGO should be informed in advance of any planned incident management strategy, in case their involvement is required.

# 11 References

1. Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95) - annotated with TGA comments. July 2000 http://www.tga.gov.au/industry/clinical-trials-note-ich13595.htm (accessed 10Nov15)
2. NSW Health Guideline GL2010_014 : Operations Manual: Human Research Ethics Committee Executive Officers http://www.health.nsw.gov.au/policies/gl/2010/pdf/GL2010_014.pdf (accessed 10Nov15)
3. Therapeutic Goods Administration. Access to Unapproved Therapeutic Good – Clinical Trials in Australia. October 2004. http://www.tga.gov.au/industry/clinical-trials-guidelines.htm (accessed 10Nov15)
4. Note for Guidance on Clinical Safety Data Management Definitions and Standards for Expedited Reporting (CPMP/ICH/377/95) –annotated with TGA comments. July 2000 http://www.tga.gov.au/industry/clinical-trials-note-ich37795.htm (accessed 10Nov15)
5. Therapeutic Goods Administration. The Australian Clinical Trials Handbook. March 2006. http://www.tga.gov.au/industry/clinical-trials-handbook.htm (accessed 10Nov15)
6. NHMRC. The National Statement on Ethical Conduct in Human Research. 2007 (National Statement). http://www.nhmrc.gov.au/publications/synopses/e72syn.htm (accessed 10Nov15)
7. NSW Policy Directive PD2010_055. Research - Ethical & Scientific Review of Human Research in NSW Public Health Organisations. http://www.health.nsw.gov.au/policies/pd/2010/pdf/PD2010_055.pdf (accessed 10Nov15)
8. NSW Health Guideline GL2011_001: Research Governance in NSW Public Health Organisations http://www.health.nsw.gov.au/policies/gl/2011/pdf/GL2011_001.pdf (accessed 10Nov15)
9. NSW Health Guideline GL2010_015: Operations Manual: Research Governance Officers http://www.health.nsw.gov.au/policies/gl/2010/pdf/GL2010_015.pdf (accessed 10Nov15)
10. NSW Policy Directive PD2014_004: Incident Management http://www0.health.nsw.gov.au/policies/pd/2014/pdf/PD2014_004.pdf (accessed 10Nov15)
11. The International Compilation of Human Research Standards http://www.hhs.gov/ohrp/international/intlcompilation/intlcompilation.html (accessed 10Nov15)
12. The NHMRC Australian Health Ethics Committee (AHEC) Position statement: Monitoring and reporting of safety for clinical trials involving therapeutic products. May 2009 http://www.nhmrc.gov.au/_files_nhmrc/file/health_ethics/hrecs/reference/090609_nhmrc_position_statement.pdf (accessed 10Nov15)

# 12 Appendix: Safety reporting responsibilities and requirements for trials conducted at SCHN

**Notes:**

* In the event of a multi-centre investigator-initiated clinical trial where SCHN is one of many sponsors around the country, the trial team should have an agreement defining which site PI is responsible for safety reporting to regulatory authorities. For commercially sponsored clinical trials, the commercial sponsor will take responsibility for safety reporting to regulatory authorities.

** SCHN PI refers to the PI approved by the SCHN RGO to run the trial at CHW or SCH. Where both CHW and SCH are sites, the PI of both sites must each report as required below.

*** Where the trial has not been reviewed and approved by the SCHN HREC, the CI holding the HREC approval is responsible for following the safety reporting requirements of the approving HREC (which may be different to the requirements listed below) and advising SCHN PIs of the timeliness and format of information they should provide to the CI in order to facilitate HREC reporting.

| Where event occurred | Type of Event | Who needs to report | Reports to | In what format | In what timeframe | Documentation to be kept/maintained by PI |
|---|---|---|---|---|---|---|
| Anywhere | Any safety events or information that materially impacts on the continued ethical acceptability of the trial OR requires/results in a need for a change to the trial protocol, including changed safety monitoring. | SCHN PI** | SCHN HREC*** | HREC reporting form | Within 72 hours (unless PI believes immediate notification necessary) | Site, sponsor, regulatory authority, HREC and RGO safety related documents and correspondence |
| | | | SCHN RGO | Copy of information provided to HREC | At same time that information is provided to HREC | |
| Overseas | Significant issues arising from the analysis of overseas safety reports OR action taken by an overseas regulatory agency | Sponsor* | TGA | For drugs: Blue card;<br>For devices: Medical Device Incident Report | Within 72 hrs | Site, sponsor, regulatory authority, HREC and RGO safety related documents and correspondence |

| Where event occurred | Type of Event | Who needs to report | Reports to | In what format | In what timeframe | Documentation to be kept/maintained by PI |
|---|---|---|---|---|---|---|
| Australia or Overseas | SUSARs; SUADEs<br><br>(Note: SUSARs and SUADEs are a subset of SAEs. The requirements listed here must be completed in addition to the reporting requirements for SAEs.) | Sponsor* | TGA<br>(Note: only report Australian SUSARs, SUADEs to TGA or Significant issues arising from the analysis of overseas safety reports OR action taken by an overseas regulatory agency per timelines in row above). | For drugs: Blue card;<br>For devices: Medical Device Incident Report | 7 calendar days (with FU report within a further 8 days) for fatal or life-threatening events<br>15 calendar days for all other SUSARs/SUADEs | Source documents<br>CRFs<br>TGA, HREC and RGO safety reporting correspondence (if reports made) |
| | | SCHN PI** | SCHN HREC*** | If individual event impacts study: On HREC reporting form.<br>Other: Line listing of all SUSAR/SUADEs with comment | Report individual events that impact the trial within 72hrs.<br><br>Otherwise, a line listing of all SUSARs/SUADEs should be reported every 6 months (as a minimum) including a comment regarding impact on research/action taken | |
| | | | SCHN RGO of SUSARS or SUADEs of SCHN recruited participants only. | For CTN/CTX trials: Copy of information submitted to TGA;<br>For non-CTN/CTX trials: A letter outlining event history, outcomes, impact to the trial. | Within 7 calendar days (with FU report within a further 8 days) for fatal or life-threatening events<br><br>Within 15 calendar days for all other SUSARs/ SUADEs | |
| | | | Sponsor | CRF / study specific form | As for SAE's, within 24hr | |

| Where event occurred | Type of Event | Who needs to report | Reports to | In what format | In what timeframe | Documentation to be kept/maintained by PI |
|---|---|---|---|---|---|---|
| SCHN/ Australian site | SAE (Drug or Device)<br><br>(Note: Definitions and reporting requirements for SAEs should be described in the protocol) | Sponsor* | TGA | Tabulation | Upon request (usually not required if events are expected) | Source documents<br>CRFs<br>TGA, HREC and RGO safety reporting correspondence (if reports made) |
| | | SCHN PI** | SCHN HREC*** | If individual event impacts research: On HREC reporting form.<br>Other: Summary with comment attached to HREC annual report | Report individual events that impact the trial within 72hrs.<br>(No need to report individual events within 72 hrs if there is no impact on the study).<br><br>A summary of all SAEs (including a comment regarding impact on research/action taken) should be attached to the HREC annual report (unless HREC approval stipulates specific reporting requirements) | |
| | | | CI (if not approved by SCHN HREC) | Format requested by CI | Per HREC approval conditions | |
| | | | SCHN RGO | Copy of annual report as provided to HREC | Annually | |
| | | | IIMS (Only if appropriate, per Policy10) | electronic | Timeframes dependent on severity – refer to policy10 | |
| | | | Sponsor* | CRF / study specific form | Within 24 hours (unless otherwise stated in protocol). | |

| Where event occurred | Type of Event | Who needs to report | Reports to | In what format | In what timeframe | Documentation to be kept/maintained by PI |
|---|---|---|---|---|---|---|
| SCHN/ Australian site | AE (Drug); ADE<br><br>(Note: The AEs targeted for reporting should be described in the protocol) | Sponsor* | TGA (for CTN/CTX studies only) | Tabulation | Upon request | Source documents CRFs<br>TGA, HREC and RGO safety reporting correspondence (if reports made) |
| | | SCHN PI** | SCHN HREC*** | HREC reporting form | No need to report unless impact on study and action is required (see row 1). | |
| | | | CI (if not approved by SCHN HREC) | Format requested by CI | Per HREC approval conditions<br>(usually not required) | |
| | | | SCHN RGO | Not required | Upon request | |
| | | | Sponsor* | CRF / study specific form | Per protocol/study specific procedures | |
| Not related to a single event | Updated investigator brochure (IB), EU annual safety report (or similar) or current Australian Product Information or other reports consistent with National Statement section 5.5.5 or GCP. | SCHN PI** | SCHN HREC*** | HREC – For information with a cover letter and statement re impact on trial. | When updated IB, product information or annual EU safety report received. | Sponsor and HREC safety related documents and correspondence |