

# Policy Statement



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## Adverse Events: Definitions, Recording and Reporting

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**Summary:** The aim of this policy statement is to provide definitions and general recording and reporting requirements for adverse events.

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**Applies to:** TROG Trial Sites, TROG Trial Coordinating Centres, Trial Management Committees, Independent Data Safety Monitoring Committees, TROG Scientific Committee and TROG Central Operations Office

**Approved by:** TROG Scientific Committee

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**Revision Chronology:** Vs 1: 21 June 1999 New Policy

Vs 2: 05 Sept 2008 Updated in accordance with current regulatory guidelines and specific TROG requirements

Vs 3: 25 July 2012 Updated in accordance with current regulatory guidelines and specific TROG requirements

Vs 4: 28 April 2015 Incorporation of adverse device event reporting. Procedures and timeframes removed to avoid duplication and misunderstanding between policy and protocols.

## CONTENTS

1. INTRODUCTION .....	3
2. ADVERSE EVENT DEFINITIONS – MEDICINES.....	3
2.1 Adverse event.....	3
2.2 Adverse Drug Reaction .....	3
2.3 Unexpected Adverse Drug Reactions.....	3
2.4 Serious Adverse Event or Adverse Drug Reaction.....	4
2.5 Unexpected Adverse Drug Reaction .....	4
3. ADVERSE EVENT DEFINITIONS - MEDICAL DEVICES .....	5
3.1 Medical Device .....	5
3.2 Adverse Device Event.....	5
3.3 Unanticipated Device Related Adverse Event.....	5
3.4 Serious Adverse Device Event .....	6
4. RECORDING AND REPORTING .....	6
4.1 Adverse Events .....	6
4.2 Serious Adverse Events .....	7
5. ETHICS AND GOVERNANCE.....	7
6. REFERENCES.....	8

## **1. INTRODUCTION**

When conducting clinical trials the rights, safety and wellbeing of the trial participants are the most important considerations and should prevail over the interests of science and society<sup>1</sup>.

Adverse event reporting for medicines or medical devices in clinical trials is fundamental in detecting patient safety problems and in determining any necessary action required by the researchers or, in some cases, the regulatory authorities.

This policy statement is issued in accordance with the Note for Guidance on Clinical Safety Data Management: Definitions and Standards for Expedited Reporting (annotated with TGA comments)<sup>2</sup> and the TGA Australian regulatory guidelines for medical devices (ARGMD)<sup>3</sup>, and has been developed to assist TROG researchers in understanding the categories of adverse events (medicines and medical device) and the adverse event recording and reporting path.

## **2. ADVERSE EVENT DEFINITIONS – MEDICINES**

### **2.1 Adverse event**

Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment.

An AE can therefore be any unfavourable and unintended sign (including any abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered to be related to the product.

### **2.2 Adverse Drug Reaction**

In the *pre-approval clinical experience* with a new medical product or its new usages, particularly as the therapeutic dose(s) may not be established: all noxious and unintended responses to a medicinal product related to any dose should be considered adverse drug reactions. A causal relationship between the adverse event and the medicinal product cannot be ruled out<sup>2</sup>.

With regards to marketed medical products: a response to a drug which is noxious and unintended and which occurs at doses normally used in human for prophylaxis, diagnosis, or therapy of diseases or for modification of physiological function.

### **2.3 Unexpected Adverse Drug Reactions**

An adverse reaction, the nature or severity of which is not consistent with the applicable product information. Product information can be in the Investigator's Brochure (IB) for an unapproved investigational product or the Product Information leaflet for an approved product<sup>1</sup>.

## 2.4 Serious Adverse Event or Adverse Drug Reaction

Adverse events and adverse drug reactions are considered 'serious' if they threaten life or function. Due to the significant information they provide, Serious Adverse Events (including Serious Adverse Drug Reactions) require expedited reporting.

SAEs are defined as any adverse event or adverse drug reaction which:

- Results in death
- Is life-threatening
- Requires In-Patient Hospitalisation or Prolongation of Existing Hospitalisation
- Results in Persistent or Significant Disability/Incapacity, or
- Is a Congenital Anomaly/Birth Defect

The term 'life-threatening' in the definition of 'serious' refers to an event in which the participant was immediately at risk of death at the time of event. It does not refer to an event which hypothetically might have caused death if it were more severe. However, important medical events may be considered a serious adverse experience if they require medical or surgical intervention to prevent one of the listed definitions, e.g. an 'allergic bronchospasm' which required intensive treatment in an emergency room or at home.

An event that results in hospitalisation or prolongs an existing hospitalisation will not be considered a SAE if the only reason for the hospitalisation or prolongation was:

- administration of chemotherapy
- administration of trial procedures
- placement of a permanent intravenous catheter
- hospice placement for terminal care
- pre-trial scheduled elective surgery
- out-patient hospitalisation for procedures such as:
- Elective day surgery
- Convenience purposes (e.g. transportation difficulties)
- Admission for insertion of PEG tube or naso-gastric tube for commencement of enteral feeding.

## 2.5 Unexpected Adverse Drug Reaction

An "unexpected" adverse reaction is one, the nature or severity of which is not consistent with the applicable product information (e.g. Investigators Brochure for an unapproved investigational medical product)

### **3. ADVERSE EVENT DEFINITIONS - MEDICAL DEVICES**

#### **3.1 Medical Device**

The Therapeutic Goods Act 1989<sup>4</sup> defines a medical device as:

- a. any instrument, apparatus, appliance, material or other article (whether used alone or in combination, and including the software necessary for its proper application) intended, by the person under whose name it is or is to be supplied, to be used for human beings for the purpose of one or more of the following:
  - i. diagnosis, prevention, monitoring, treatment or alleviation of disease;
  - ii. diagnosis, monitoring, treatment, alleviation of or compensation for an injury or disability;
  - iii. investigation, replacement or modification of the anatomy or of a physiological process;
  - iv. control of conception;
  - v. and that does not achieve its principal intended action in or on the human body by pharmacological, immunological or metabolic means, but that may be assisted in its function by such means; or
    - aa. any instrument, apparatus, appliance, material or other article specified under subsection (2A); or
    - ab. any instrument, apparatus, appliance, material or other article that is included in a class of instruments, apparatus, appliances, materials or other articles specified under subsection (2B); or
- b. an accessory to such an instrument, apparatus, appliance, material or other article covered by paragraph (a), (aa) or (ab).

#### **3.2 Adverse Device Event**

An adverse device event is defined as a clinical sign, symptom or condition that is causally related to the device implantation procedure, the presence of device, or the performance of the device system.

#### **3.3 Unanticipated Device Related Adverse Event**

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)

### **3.4 Serious Adverse Device Event**

Serious Adverse Events (SAEs) in medical device trials are defined as any adverse medical occurrence that:

- Led to 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 or increased length of existing hospitalisation
  - A condition requiring unnecessary medical or surgical intervention
  - Foetal distress, foetal death or a congenital abnormality/ birth defect
- Might have led to death or a serious deterioration in health had suitable action or intervention not taken place. This includes:
  - A malfunction of a device such that it has to be modified or temporarily/ permanently taken out of service
  - A factor (a deterioration in characteristics or performance) found on examination of the device.

## **4. RECORDING AND REPORTING**

Adverse event reporting procedures for TROG trials may differ between trials depending on the intervention. As such, this policy explains general requirements on the identification, recording and reporting of adverse events and serious adverse events. Please refer to the trial protocol for specific trial AE/SAE reporting procedures.

### **4.1 Adverse Events**

All adverse events regardless of their severity or expectedness must be recorded in the patients' medical records.

Non-serious or expected adverse reactions will be transcribed from the medical records onto trial specific adverse event case report forms (CRFs) or entered onto the online electronic CRFs (eCRFs). Adverse event data shall be transferred from the CRFs into the trial database and analysed by the Trial Management Committee and/or an Independent Data Safety Monitoring Committee (IDSMC) at time points specified in the protocol.

Line listings of adverse events shall be made available to the Therapeutic Goods Administration (TGA) upon request.

## 4.2 Serious Adverse Events

For *medicine* related adverse events the principal investigator is responsible for identifying the seriousness of the adverse event and, if deemed serious, identifying the causal relationship and determining the expectedness according to the Product Information and/or Investigators Brochure.

For *device* related SAEs, the principal investigator is responsible for identifying the seriousness of the adverse event and submitting an SAE report to the TROG Trial Coordinating Centre who shall arrange for the chairperson and/ or a clinical reviewer to review the submitted SAE report in the context of information known about the medical device and make a determination as to whether the event was device related and if so, if it was an anticipated event.

All serious adverse events must be reviewed by a clinical reviewer as delegated by the Trial Management committee prior to submission to ethical and regulatory bodies.

In either case, if the serious adverse event is suspected to be *unexpected* and *related* to the medicine or medical device, the event must be reported, by TROG, in an expedited manner to the TGA in Australia and (if required) Medsafe in New Zealand. **Specific timeframes and procedures for reporting will be detailed in each trial protocol.**

There may be a situation where a *non-serious* or an *expected* SAE requires rapid reporting to the regulatory authorities. Appropriate scientific judgement for reporting should be applied under the following circumstances;

- a) For an 'expected' SAE, an increase in the rate of occurrence which is judged to be clinically important
- b) A significant hazard to the patient population such as lack of efficacy with a medicinal product or intervention used in treating life threatening disease.
- c) A major safety finding from a newly completed animal study (such as carcinogenicity).

SAEs must continue to be reported on until the event has been resolved or until participant's death.

## 5. ETHICS AND GOVERNANCE

All trial sites that submit ethics applications (i.e. lead ethics sites for multicentre ethical review and sites submitting for single ethical review) are responsible for clarifying the SAE reporting requirements for the approving Humans Research Ethics Committees (HRECs) and coordinating the submission of relevant reports and line listings according to the HRECs guidelines.

Principal Investigators at each trial are responsible for determining if the approving Research Governance Office requires local SAEs to be reported and coordinating the submission of relevant reports accordingly.

## 6. REFERENCES

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