



Trans Tasman Radiation Oncology
Group Limited
ACN 132 672 292

TROG POLICY AND PROCEDURES

Adverse Event Definitions, Scoring and Reporting

TPP E4

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(Always refer to the TROG website to check for the current version of this policy)

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1. Introduction

When conducting clinical trials, it is important that Adverse Events (AEs) are monitored in the interest of patient safety. The investigator at each trial site is responsible for assessing and reporting AEs as part of routine clinical monitoring and data collection. During the trial, the Trial Management Committee (TMC) and/or the Data Monitoring Committee (DMC) monitor AEs so that safety profiles can be established. While the majority of AEs that occur during a trial will be considered 'routine', a small subset will be classified as serious (Serious Adverse Events - SAEs) and will require expedited reporting to the Trial Coordinating Centre (TCC), TROG Central Operations Office (TCOO) and relevant government regulatory authorities (if drug/device related).

In order to also monitor the safety of radiotherapy in trials, TROG has resolved that, the definitions below will also apply for radiotherapy reactions. SAEs relating to radiotherapy reactions are not required to be reported to the regulatory authorities however they must be reported to the responsible Human Research Ethics Committees (HREC), the TCC and the TCOO. Each trial site should clarify reporting requirements with their HREC.

2. Adverse Event Definitions

2.1 Adverse Event (AE)

An adverse event is defined in ICH GCP guidelines as '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.'¹

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 (ADR)

An Adverse Drug Reaction is defined in ICH GCP Guidelines as;

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'

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

2.3 Unexpected Adverse Drug Reaction

An adverse reaction, the nature or severity of which is not consistent with the applicable product information eg. Investigator's Brochure for an unapproved investigational product or Product Information/package insert for an approved product.

2.4 Serious Adverse Event (SAE)

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 (i.e. fatal/grade 5 CTC AE)
(Note: In the context of TROG trials, death due to cancer is considered 'expected' and is therefore not a SAE)
- Is life-threatening (i.e. grade 4 CTC AE)
- 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 (eg. transportation difficulties)
 - Admission for insertion of PEG tube or naso-gastric tube for commencement of enteral feeding.

Overdoses (drug or radiation) should be reported in an expedited fashion if the events associated with the overdose meet the SAE definitions listed above. If no SAEs are experienced the overdose will not require expedited reporting however will need to be reported to the TCC on the relevant trial Case Report Forms.

The development of new cancers at any time during the trial follow-up period should be reported on the relevant trial forms. If any events associated with the new cancer meet the SAE definitions listed above, then they should also be reported in an expedited fashion.

3. Adverse Event Scoring

Grading of all recorded adverse events (including ADRs and SAEs) should be carried out according to an agreed international scale.

TROG endorses the Common Terminology Criteria for Adverse Events v3.0 (CTCAE). The CTCAE incorporates not only radiation related adverse events but also haematological and other chemotherapy related events. Relevant sections of the CTCAE must be included in the protocol and case report forms. The CTCAE can be downloaded from the CTEP website (<http://ctep.cancer.gov/forms/CTCAEv3.pdf>)

For consistency, grading should preferably be performed by the same person throughout the trial. If no existing scale is found for a specific adverse event, a grading system must be defined in the protocol.

4. Reporting

4.1 Adverse Event Reporting

Non-serious or *expected* adverse reactions should be recorded on the relevant trial Case Report Form(s) and be available for analysis at the completion of the trial. Documentation of an adverse event requires specific information regarding the sign, symptom or disease.

4.2 Adverse Drug Reaction Reporting

All ADRs that are both *serious* and *unexpected* are to be reported to the appropriate regulatory authorities according to Serious Adverse Event reporting procedures (refer to 4.3.2.1 and 4.3.2.2).

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

- a) For an 'expected' serious ADR, 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 used in treating life threatening disease.
- c) A major safety finding from a newly completed animal study (such as carcinogenicity).

4.3 Serious Adverse Event Reporting

4.3.1 Trial Sites/Investigators

Investigators are required to adhere to expedited reporting guidelines for SAEs as specified in the safety reporting section of the trial protocol. Refer to Appendix 1 for a summary of the procedures. The standardised TROG SAE Report form (refer to Appendix 4) should be submitted, in accordance with the timelines stipulated in the protocol, to the Trial Coordinating Centre, the TROG Central Operations Office, the pharmaceutical/device company (if applicable) and the responsible Human Research Ethics Committee (HREC).

4.3.2 Trial Coordinating Centre

Formal procedures for the immediate clinical review of SAEs by a qualified person should be in place at the TCC to ensure any safety issues and subsequent actions are identified as soon as possible. Refer to Appendices 2 and 3 for responsibilities and timeline.

4.3.2.1 SAE Reporting – Australian Regulatory Authorities

If the Trial Chairperson and the Principal Investigator consider that the SAE is drug related and **unexpected** (according to the definitions presented above), it should be reported to the Experimental Drugs Section, Drug Safety and Evaluation Branch of the Therapeutic Goods Section (TGA) by the Trial Coordinating Centre within 7 days if fatal or life-threatening or 15 days if not (refer to Appendix 2).

For post-marketing clinical trials of medicines used *within* marketing approval all adverse event reporting should occur directly to the Adverse Drug Reaction Unit of the TGA, not the Experimental Drugs Section of the Drug Safety and Evaluation Branch².

Clinical Trial Notification (CTN) scheme: For trials conducted under this scheme, appropriate supporting information such as the trial protocol should also be submitted with the SAE report.

Serious adverse events that occur as part of an international arm of a trial (ie. at overseas sites) being conducted in Australia by TROG are not required to be reported to the TGA. These SAEs are to be evaluated by the TMC/DMC and TSC and should the information significantly affect the risk/benefit ration of a drug/device, the information should be communicated to the TGA within 72 hours of first knowledge.

All serious and **unexpected** adverse device events should be reported to the Office of Devices, Blood and Tissues of the TGA with the same timelines as for SAE drug reactions. Refer to 'Access to Unapproved Therapeutic Goods - Clinical Trials in Australia, TGA, October 2004'³ for definitions of SAE device adverse events.

4.3.2.2 SAE Reporting - New Zealand Regulatory Authorities

The NZ Good Clinical Research Practice Guidelines⁴ state that the investigator is to report all SAEs which result in the unblinding of the study code, except where an event is a specific end point of the study to the sponsor (ie. TROG Trial Coordinating

Centre) within 3 working days. Other SAEs should be reported to the sponsor within either 15 working days or the timeline defined in the protocol. The sponsor is responsible for reporting all serious adverse events which result in the breaking of the study code to the regulatory authority (Medsafe) within 72 hours. The sponsor is only required to report to the regulatory authority an analysis of all SAE reports received from investigators in New Zealand.

All other SAEs which do not result in breaking the study code and which are not specified as study end points, should be recorded and presented to the Ethics Committees and/or regulatory authority as part of the regular reporting requirements of these bodies. The report from the sponsor should contain an analysis of the unblinded serious adverse events reports for the investigational product(s) with respect to possible causality and impact on the continuation of the trial

5. TROG Standardised Protocol Section

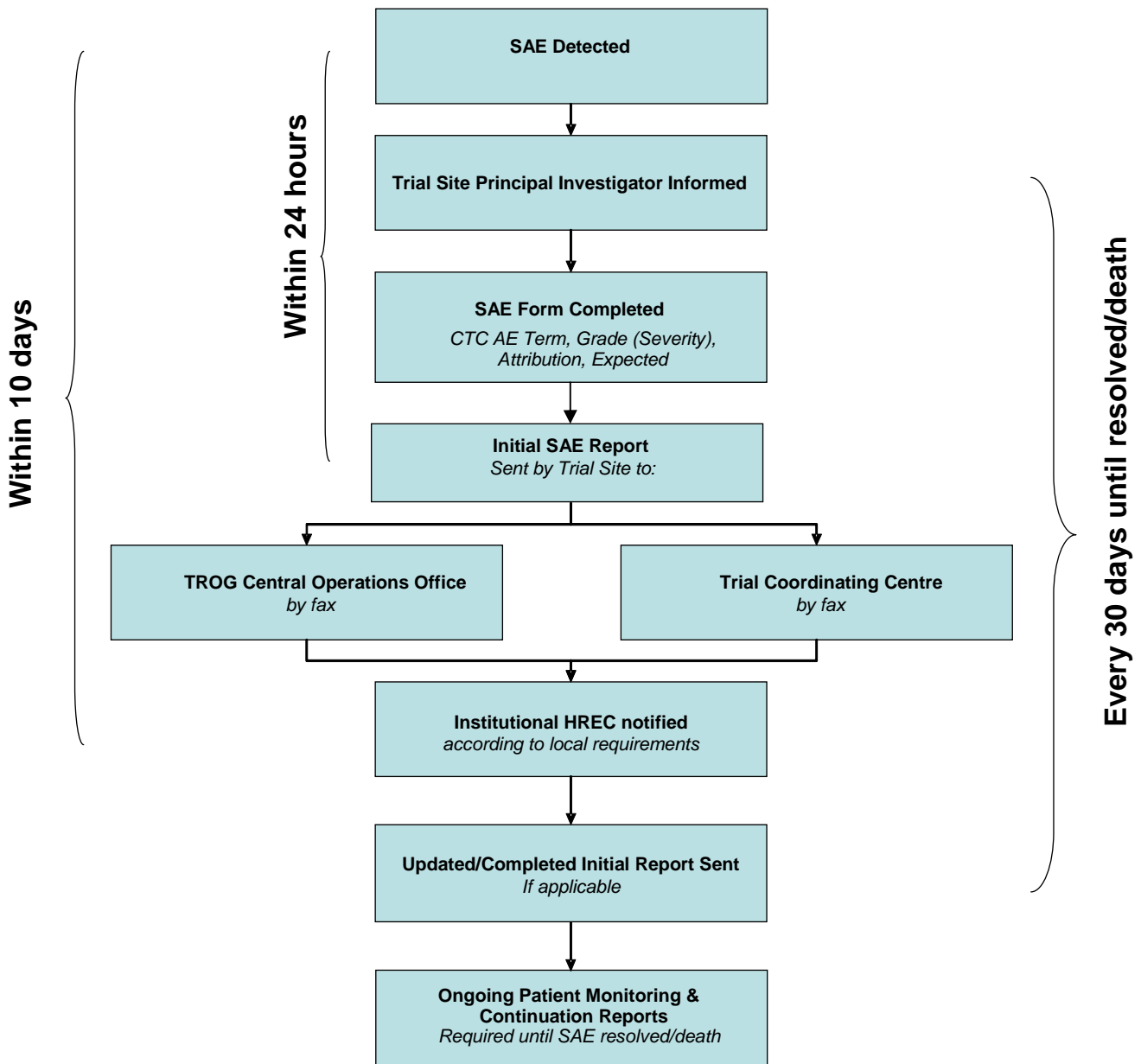
When drafting a TROG protocol, the 'Adverse Event Scoring and Reporting' section of the TROG protocol template must be used. This standard section can be adapted to include trial specific information such as contact details for the Trial Coordinating Centre.

6. References

1. Note for Guidance on Clinical Safety Data Management: Definitions and Standards for Expedited Reporting (CPMP/ICH/377/95). Annotated with TGA comments. Therapeutic Goods Administration, Australia, July 2000. Available at <http://www.tga.gov.au/ct/index.htm>
2. The Australian Clinical Trial Handbook, March 2006. Available at <http://www.tga.gov.au/ct/cthandbook.htm>
3. Access to Unapproved Therapeutic Goods- Clinical Trials in Australia, TGA, October 2004. Available at <http://www.tga.gov.au/docs/html/clintrials.htm>4. New Zealand Regulatory Guidelines for Medicines, Interim Good Clinical Research Practice Guidelines–(Medsafe, August 1998). Available at <http://www.medsafe.govt.nz/profs/Rlss/clinical.asp>

Appendix 1

Trial Site / Principal Investigator Procedures For Reporting Serious Adverse Events (SAEs)

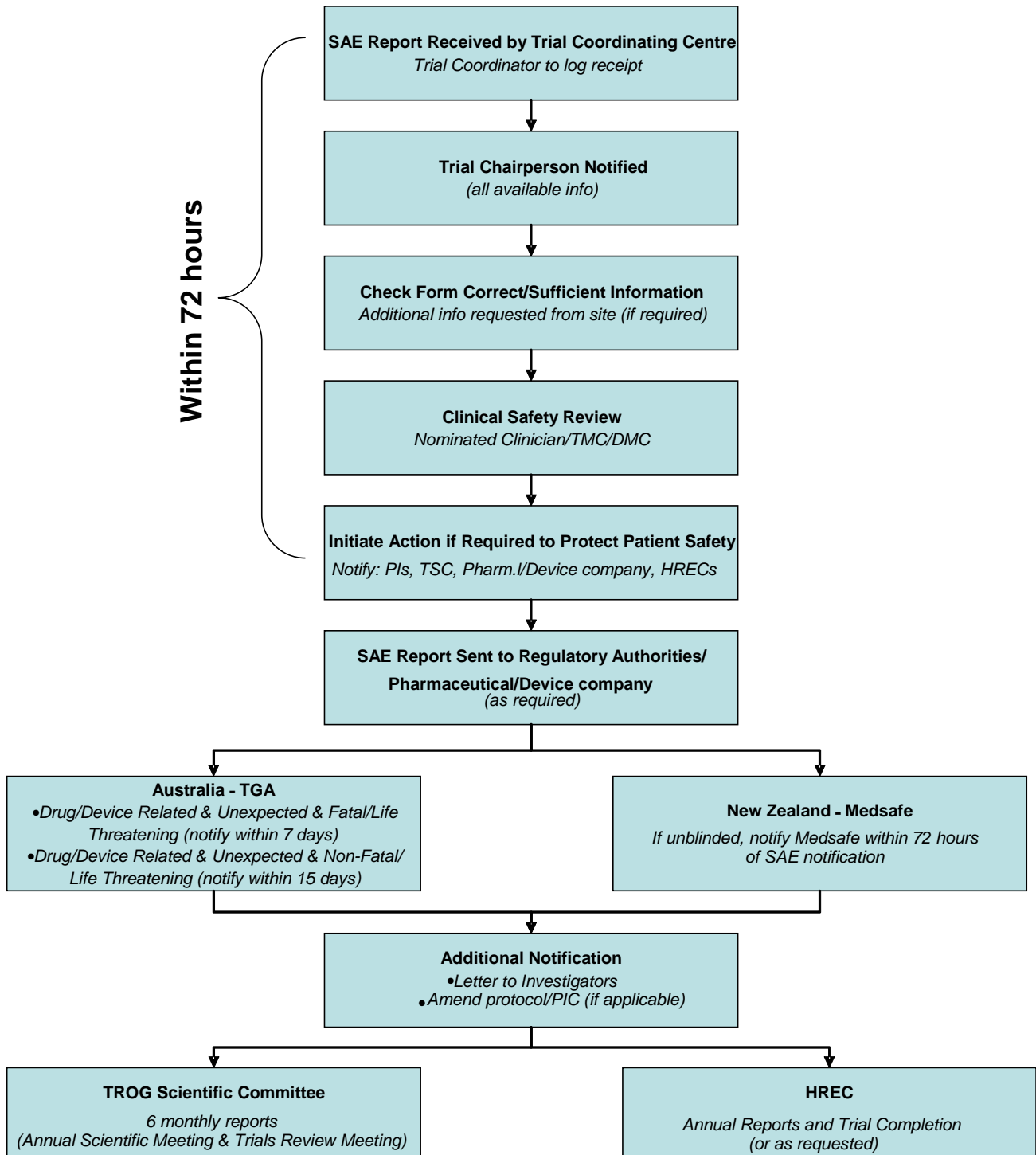


The reporting period for SAEs is from registration/randomisation of a patient, until 30 days have elapsed since their last protocol treatment/intervention. Trial sites should only change their reporting requirements if specifically requested in a trial protocol or due to local HREC requirements, e.g. reporting period of 90 days post treatment required

Appendix 2

Trial Coordinating Centre (TCC) Procedures For Reporting Serious Adverse Events (SAEs)

The Trial Coordinating Centre is responsible for pharmacovigilance and the arrangements for recording, assessing, reporting, analysing and managing adverse events. The procedures below demonstrate how these responsibilities are performed.



Trans Tasman Radiation Oncology Group
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Appendix 3

**TRIAL COORDINATING CENTRE MANAGEMENT OF SERIOUS ADVERSE EVENTS (SAEs)
Guidelines for Safety Reporting Procedures**

1. Trial Coordinating Centre (TCC) to maintain database/log of all SAE reports received eg. Collate information from individual SAE reports in table format (example below). The 'quality check' is approved if sufficient data is available for the reviewer to assess each SAE.

SAE Ref N ^o	Reg N ^o	Centre	Date of Onset	Date SAE Reported	AE Description (CTCAE & Grade)	SAE Type	Causality	Outcome	Unexpected	Trial Centre SAE Form Quality Check	Date Reviewed by TMC Rep	Expedited Report Sent to Sites	Expedited Report Sent to Regulatory Authorities
1	XXX	LMH	01/06/2003	02/06/2003	Infection – wound (Grade 3)	Hospitalisation	Study Drug (Cisplatin)	Resolved	[YES/NO]	√	05/06/2003	[YES /N/A]	[TGA/ CARM / N/A]
2													

2. TCC to ensure up-to-date reports are available for Data Monitoring Committee (DMC)/Trial Management Committee (TMC) or representative/s for review as required (eg. as SAEs are received)
3. DMC/TMC to review SAEs – Documentation should include (example of review log below):
 - Verify Classification of 'Expected' or 'Unexpected' (*ie. nature and severity of event IS/IS NOT consistent with applicable/known product or treatment information*): agree with site documentation of expected/unexpected nature of event
 - Provision of summary review comment including an 'action' recommendation
 - Date reviews were conducted

Date of Review	SAE Ref N ^o s	Reviewers	Reviewer Comments	Clinical Safety Action Statement
30/06/2003	# 1-6	DA, JH	No additional information necessary	Trial to continue – no modifications required

4. DMC/TMC determines if expedited reporting is necessary (SAEs classified as 'unexpected'):

ie. "the sponsor should promptly notify all concerned investigator(s), institution(s) and regulatory authority(ies) of findings that could affect adversely the safety of subjects, impact the conduct of the trial, or alter the IRB/IEC's approval/favourable opinion to continue the trial." [TGA/GCP]

- Expedited reporting is required if an SAE is 'unexpected', that is, not consistent with the current known product or treatment information (eg. not listed in the Australian Product Information and/or Investigators Brochure) but suspected to be due to the product or treatment, or if the reaction does appear in the API or IB but is described as having no established causal relationship, or the event is listed in the API or IB but is noted to be more severe than described in the available information.
- If expedited reporting is required the TCC must provide a summary SAE report (with site identifier information removed, eg. use SAE Ref No and/or participant identification number without treatment centre name) to all Trial Sites, who must then forward the reports on to their institutional Human Research Ethics Committee/s.
- Unexpected drug-related SAEs arising during a clinical trial from an Australian site must be reported to the TGA within 7-15 days (refer to section 4.3.2.1) (regardless of whether the report is for the investigational drug, registered over-the-counter or listed drugs or registered prescription drugs). The ADRAC 'blue card' [see attachment 1] or an alternative format containing the same information should be used for expedited reporting of SAEs to the TGA. In addition, the trial centre should *"advise the TGA within 72 hours of any significant issue that has arisen from its analysis of overseas reports or action which has been taken by another country's regulatory agency"*. A copy of this notification should also be sent to the TROG Central Operations Office.
- Unexpected drug-related SAEs occurring in New Zealand sites must be reported to Medsafe via the Centre for Adverse Reactions Monitoring (CARM) using their reporting form [see Attachment 2]. In addition, trial centres are required to report to CARM any: investigations of safety issues by an overseas regulatory authority, new or revised safety information necessitating a change in a product data sheet, any emergent medicine-safety concerns and/or any proposed "Dear Doctor/Health Professional" letters (prior to the letter being distributed).

5. If expedited reporting is not required, the TCC should periodically (eg. 6 monthly) provide SAE summary reports (Periodic Safety Update Reports) for distribution to all investigators (and Trial Coordinators). When collating summary reports the TCC should consider:

- removal of site identifier information (eg. use SAE Ref No and/or participant identification number without treatment centre name)
- including relevant additional information (such as current total accrual, TMC comments and action recommendation from review log)
- Site Principal Investigators are responsible for forwarding periodic reports to their Human Research Ethics Committee in accordance with local requirements
- Periodic SAE reports for the trial can be used to meet bi-annual reporting requirements for the TROG Scientific Committee.

Appendix 4

The TROG Serious Adverse Event Report Form, as varied from time to time,
can be accessed through the TROG Website:

www.trog.com.au