



Standard Operating Procedures

5.17 Adverse Event Reporting ©2007

History			
Version	Date	Author	Reason
1.1	10 th Jan 2006	Contributing authors	New procedure
1.2	25 th Feb 2007	S Whicker	Administrative update
1.3	17 th July 2007	B Fazekas	Update prior to MAB review
1.4	18 th August 2007	B Fazekas	Changes ratified by MAB, and external review
1.5	16 th October 2007	B Fazekas	Update following David Currow review

Approval				
Version	Author	Signature	Approval Name	Approval Signature
1.5	B Fazekas	<i>B. Fazekas</i>	D Currow (CI)	<i>David Currow</i>

Scheduled review

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Responsible person PaCCSC National Project Officer

5.17 Adverse Event Reporting

Purpose

The safety of and burden on participants is paramount in the conduct of clinical trials. All trials are required to monitor the amount of harm that might be done to participants as a result of participation.

The purpose of this SOP is to ensure that adverse and serious adverse events of studies conducted under the Palliative Care Clinical Studies Collaborative are defined, recorded, reported and evaluated as required by Hospital Research Ethics Committees (HRECs) and the ICH guidelines.

Other related SOPs

Protocol Development

Attachments

Reporting flow chart
Adverse Events Form
Common Toxicity Criteria

References

NHMRC National Statement on Ethical Conduct in Research Involving Humans 1999 (accessed 250207) http://www.nhmrc.gov.au/publications/_files/e35.pdf

Guideline for Good Clinical Practice ICH Harmonised Tripartite 1996 (accessed 250207) <http://www.ich.org/LOB/media/MEDIA482.pdf>

Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95). Annotated with TGA comments 2000 (accessed 250207)
<http://www.tga.gov.au/docs/pdf/euguide/ich/ich13595.pdf>

Note for Guidance on Clinical Safety Data Management: Definitions and Standards for Expedited Reporting. 2000 (accessed 250207)
<http://www.tga.gov.au/docs/pdf/euguide/ich/ich37795.pdf>

Common Toxicity Criteria (<http://ctep.info.nih.gov>)

Definitions

Adverse Event (AE)

Any untoward or unexpected occurrence in a patient or clinical investigation participant where the occurrence does not necessarily have a causal relationship with the study intervention.

An adverse event can therefore be any unfavourable, unusual and unintended sign, response, symptom, or disease where the outcome was not expected and has negative consequences for the patient or the caregiver. This can include such events as:

- an abnormal laboratory finding
- an abnormal or unusual emotional or cognitive response
- distress caused by the burden of the intervention or by participation and can occur:
 - during a study, if absent at baseline
 - or if present at baseline, appears to worsen – after completion of a person's participation in a study but as a direct result of it
- distress could also occur outside of clinical investigations in settings such as focus groups or questionnaire response
- a response or reaction that was not anticipated.

There are circumstances where adverse events are not reported.

Examples may include;

- An expected effect from a study intervention, such as constipation in opioid studies unless the side effect required additional treatment or assessment
- Signs or symptoms associated with the disease or disorder under study, unless they are more severe than expected.
- Admission to hospital for caregiver fatigue

Adverse Drug Reaction (ADR)

Drugs, or medicines, are routinely trialled prior to general release to establish therapeutic dose, safety and efficacy, or to test the drug outside of the registered use. During such a trial, any noxious and unintended response to the drug product related to any dose should be considered an adverse drug reaction.

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

In effect, any unintended response during a trial of a drug or medicine should be regarded as an adverse drug reaction or event.

The reaction should be considered **unexpected** where the nature or the severity is inconsistent with the product information or the investigators brochure

Serious Adverse Event (SAE) or Serious Adverse Drug Reaction (Serious ADR)

Any untoward medical occurrence that

- results in death
- results in attempted suicide
- is life-threatening

(These events require rapid reporting on the day they are recognised)

- requires inpatient hospitalisation or prolongation of existing hospitalisation
- results in persistent or significant disability/incapacity,
- requires ongoing medical or professional attention
- are judged to represent significant hazard

(These events are still serious but not required to be reported with the same speed as those above)

There are circumstances where adverse events are not reported.

Examples are;

Planned surgery or medical intervention that was known at the start of the study (screening) for a pre-existing condition. By contrast, if this elective admission is extended due to some unexpected occurrence this admission, this becomes a serious adverse event and should be reported.

Non Serious or Expected Adverse Event

Non-serious or expected adverse events should be recorded and reported within the PaCCSC participating sites in accordance with the ICH Good Clinical Practice guidelines. These events are to be reported to the local HREC as part of the annual reporting requirements, and also aggregated by the Coordinating Agency.

For the purposes of PaCCSC these events might include expected death in the palliative care setting, if the study requires participation or follow-up to death, or where death is expected as part of the disease trajectory, and where death is attributed to the underlying disease or sequelae.

Each study protocol should clearly state the conditions and events that would be excluded from the definition of an AE or SAE and those which constitute a non-serious or Expected Adverse Event.

Relatedness of Adverse Event to an Intervention

The site investigator should include in the report the best estimate of the relationship between an intervention and an adverse event. A guide to grading the degree of certainty about such a relationship is available at www.niaid.nih.gov/ncn/sop/adverseevents.htm. A summary of the grading is as follows:

- Unrelated** Where the adverse event is clearly not related
- Unlikely** Where the adverse event does not have a clear relationship to the intervention
- Possible** Where the adverse event follows a known pattern of response
- Probable** Where the adverse event reduces or ceases with withdrawal of the intervention or has a close temporal relationship to the intervention's introduction and is clinically plausible
- Definite** Where the adverse event ceased with withdrawal of the intervention or is an incontrovertible temporal relationship to the introduction of the intervention .

Toxicity

Where possible, the toxicity grade of the event should be established. The Common Toxicity Criteria (<http://ctep.info.nih.gov>) are recommended and the relevant sections should be included in study protocols and CRF's.

Site Investigator

The investigator at each site where the study is being conducted who takes responsibility for the conduct of the study. This might be a named investigator in the study protocol, a PaCCSC investigator (named on the grant submission), or an investigator who has been delegated responsibility by the site investigator (sub investigator).

IEC/HREC

Institutional Ethics Committee/Hospital Research Ethics Committee. This is the committee who have the authority to review and approve research studies involving human subjects.

Procedure

Responsibility

Responsibility for recording and reporting of adverse events rest with the investigator at the site, site study coordinator, and the National Manager.

Recording

Recording of adverse events will be specified by the study protocol. Each site must use the forms and processes specified by their local IEC/HREC.

All reports should identify the participants by the study ID number assigned on enrolment to the study.

In addition, all events and reactions must be reported using the online reporting form via www.caresearch.com.au.

Site Study Coordinator Reporting

The site coordinator will usually become aware of an event via the study nurse, who will have collected data and/or been in touch with the patient.

On notification from the study nurse, the site study coordinator should ensure all serious adverse events are reported to all concerned site investigators (who will assess the event) and institutions, and the National Manager within the specified timeframes.

The site coordinator should also report the event to their own IEC/HREC using locally determined report forms and timeframes.

Investigator Reporting

Site Investigators are responsible for ensuring that all reportable events are reported in the manner required by national and international regulations. The site investigator is required to assess each event for seriousness, relatedness (to the study intervention) and the expectedness. This assessment may be reported back to the site coordinator who will then complete the reporting process.

All adverse events and serious adverse events should be reported by the site investigator **immediately** of becoming aware of the event, **except** for those SAEs that the study protocol has identified as not needing immediate reporting. Immediate, in this setting, is defined as within 24 hours of knowledge of the event. These reports may be by fax and telephone depending on the severity of the event to both the coordinating site and the local HREC.

The initial reports should be followed promptly by detailed, written reports to the IEC/HREC for that site, with a copy to the National Manager for distribution to the Chair - Trial Management Committee, the Chair - Scientific Committee and the Data Safety & Monitoring Committee.

All Adverse Events and Serious Adverse Events (SAEs) are to be reported using the online report form on www.caresearch.com.au. This report will be automatically emailed to all sites for their own files and reporting processes. This should be complemented with a telephone call to the National Manager.

Adverse events and/or laboratory abnormalities identified in the protocol as critical to safety evaluations should be reported to the Coordinating Agency according to the reporting requirements and within the time periods specified by the Coordinating Agency within the protocol.

For reported deaths, the site investigator should supply the National Manager (as part of the Coordinating Agency) and the IEC/HREC with any additional requested information (e.g., autopsy reports and medical reports in the days or weeks leading to death).

Coordinating Agency Reporting

The National Manager should ensure that all adverse events are reported to

- All other sites for reporting to their own local IEC/HREC where required
- the Scientific Committee and the Management Advisory Board,
- the Data Safety & Monitoring Committee,
- the regulatory authorities when the adverse events are both **serious and unexpected drug reactions** or when the SAE may affect the conduct of the trial, the safety of the participants or their willingness to continue participation in the trial using the standard form for Adverse Drug Reactions Advisory Committee (ADRAC) by the National Manager only.

Reporting should be by fax or telephone prior to the development of the written report if assessed as a SAE. Written reports are to be completed and follow the faxed/telephoned report as soon as possible after the AE or SAE have been reported by the subject/patient or study staff.

Other committees

Continuation of any study can be determined by any of the following committees based on any patterns or trends that emerge over time, or when an event is determined to be critical to the review of the study protocol.

- IEC/HREC
- Scientific committee
- Data Safety Monitoring Board
- Regulatory authorities such as the Therapeutic Goods Administration via an **ADRAC Blue Card** (Adverse Drug Reactions Advisory Committee) (attached).

Follow-up Reporting

All reports that were incomplete at the time of initial report are to be followed-up as soon as possible. In most cases this to enable final outcome to be determined and reported.

It is the responsibility of each site to follow-up events until resolved, and then report this follow-up to the local HREC and the Coordinating agency.

The coordinating agency is required to report feedback, findings and recommendations from the external committees back to the Study Sites. This should be completed as soon as practical and within 28 days of the feedback. This will enable final reporting back to the local HREC by each study site.

Filing

Copies of all Adverse Event Forms are to be filed in the:

- patient clinical file
- subject study file
- investigator manual or filing system for that site
- site study coordinator files

Copies of ALL correspondence regarding an AE or SAE should also be forwarded for filing to the National Manager.

Electronic reporting

All events will be entered onto the electronic data capture system – www.caresearch.com.au for PaCCSC wide reporting.

This reporting mechanism will enable automatic email notifications of events in order to ensure timely distribution of event reports.

The procedure will be as follows.

1. Adverse Events.
 - a. The event will be reported by entering the event information onto the report form held on-line
 - b. An automatic email will be sent to
 - i. The site reporting the event, who will also complete their own local reporting requirements.
 - ii. The PaCCSC Project Officer, who will create and maintain a summary document for study sites
 - iii. The National Manager
2. Serious adverse events
 - a. The Project Officer at the coordinating site will forward the email notice to all sites
 - b. All sites will then insert this information into their local adverse event report formats and report to the local IEC/HREC as required

- c. All sites will forward to the coordinating site a copy of
 - i. The report to the local IEC/HREC
 - ii. The IEC/HREC acknowledgement
- d. This report will be used to generate an ADRAC Blue Card as required in the event of **serious and unexpected adverse drug reactions**. This will be completed by the Project Officer at the Coordinating Agency.

The sequence of events is summarised in the following table.

Event type	Expectedness	Relatedness	Report by	Report to	Timeframe	Expedited
Adverse event	Expected or unexpected	Related or unrelated	Investigator	Local HREC	As per local requirements May be <ul style="list-style-type: none"> • via annual report • to next agenda 	No
				Coordinating centre	Via Caresearch ASAP	
			Coordinating centre	All other sites for annual reporting	As soon as assessed and completed via Caresearch.	
Serious adverse event	Expected	Related or unrelated	Investigator	Local HREC	As detailed within the study protocol	No
				Coordinating centre	Via Caresearch ASAP	
			Coordinating centre	All other sites for annual reporting	As soon as assessed and completed via Caresearch.	
	Unexpected	Related	Investigator	Local HREC	Immediate, using locally required forms	Yes
				Coordinating centre	Immediate via caresearch	
			Coordinating centre	<ul style="list-style-type: none"> • All other sites • DSMB • Scientific committee 	Within 7 days of first knowledge Follow-up within further 8 days (total 15 days)	
			Investigator	Local HREC	Immediate via caresearch	
		Unrelated	Coordinating centre	<ul style="list-style-type: none"> • All other sites • DSMB 	Within 7 days of first knowledge	No

Event type	Expectedness	Relatedness	Report by	Report to	Timeframe	Expedited
				<ul style="list-style-type: none"> Scientific committee 	Follow-up within further 8 days (total 15 days)	
Adverse drug reaction	Serious and expected	Related	Investigator	Local HREC	As detailed within the study protocol and immediate via caresearch	No, unless event results in death, or is life threatening, or requires intervention to prevent death
			Coordinating centre	<ul style="list-style-type: none"> All other sites DSMB Scientific committee 	Within 7 days of first knowledge Follow-up within further 8 days (total 15 days)	
	Serious and unexpected	Related	Investigator	Local HREC	Immediate, using locally required forms and via Caresearch.	Yes
			Coordinating centre	<ul style="list-style-type: none"> All other sites DSMB Scientific committee ADRAC Blue Card 	Immediate via Caresearch to all sites, and Within 7 days of first knowledge Follow-up within further 8 days (total 15 days) using appropriate forms to other organisations.	

The investigator at each site should make sure they are familiar with the local reporting requirements of the local research ethics committee to ensure local requirements are being met.

The following table provides some information for each site. Investigators are to check for updates and changes.

Site	Reporting timeframe	Specific form required	Other requirements
Repatriation General Hospital	Immediate for SAE	Yes	AE's from other sites to be summarised monthly in specific form
Flinders Medical Centre	SAE's, when they occur	No	AE's in collated form in annual report. Does not require reports from other sites unless appropriate
Silverchain	Immediate	No	For all events that might warrant ethical review of approval
Curtin	Immediate	No	Suspend recruitment until reviewed
Braeside (Hope Healthcare)	None specified	No	
Peter MacCallum	As early as possible	No	Victorian Managed Insurance Authority also need to be notified of events due to indemnity implications (use specific form). Requires all serious and unexpected reports from other sites
Mater	Immediate	Yes, specific forms for internal and external events	Summarise SAE's from external sites monthly into template provided
Royal Prince Alfred	None specified	Yes	
Liverpool	None specified	No	

