



PaCCSC
Palliative Care Clinical Studies Collaborative

Standard Operating Procedures

6.0 Protocol development ©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	11 th July 2007	B Fazekas	Update prior to MAB review
1.4	13 th August 2007	B Fazekas	Changes ratified by MAB
1.5	16 th October 2007	B Fazekas	Update after review by David Currow

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

Scheduled review

Date August 2008

Responsible person PaCCSC National Project Officer

6.0 Protocol development

Purpose

All clinical trials must demonstrate that documentation meets the ICH GCP guidelines. The documentation should show that the trial was conducted in an ethical and appropriate manner and all legal and auditing requirements have been met. This documentation comprises the trial or study protocol and supporting documents. Clinical trials are conducted, monitored, and audited against the protocol.

This SOP describes what the protocol is, how it is developed, and how and under what circumstances it can be changed. All protocols are to be developed according to a standard procedure to ensure that the final protocol complies with all regulatory requirements and underpins a sound clinical trial.

This SOP refers to changes to the protocol while the protocol is still undergoing development, Protocol Amendments made AFTER the protocol has been finalised are covered by procedures described under the Ethics Approval and Reporting SOP.

Other related SOPs

Ethics Approval and Reporting
Version Tracking
Essential Documents

Attachments

Protocol synopsis
New protocol development flow

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>

Liu MB, Davis K. Lessons from a horse named Jim. Duke Clinical Research Institute. 2001.

TROG Policies and Procedures Manual

Medicines Australia (accessed 25/02/07) <http://www.medicinesaustralia.com.au>

DeAngelis CD, Drazen JM, Frizelle FA, et al. Clinical Trial Registration: a statement for the International Committee of Medical Journal Editors. *JAMA* 2004, 292: 1363-1364.

Definitions

Study Protocol

The study protocol is a document that provides the full and detailed description of the study; the objectives, design, methodology, statistical considerations, and organisation of the trial, such as how the study will be implemented and evaluated.

Following approval by the appropriate regulatory bodies (ethics, TGA, FDA etc), the study protocol becomes the definitive document for all aspects of the trial implementation, evaluation and reporting.

In multi-site collaborative research all participating sites must adhere to the same version of the study protocol, while there may be site specific methods for implementing the study protocol.

The study protocol forms the basis for:

- funding applications and contracts
- ethics submissions
- budget
- study evaluation and auditing
- data collection form development.

Protocol types

- *Phase I* clinical trials involve the first administration of the medicine to humans, usually to small numbers of healthy volunteers. Phase I clinical trials determine the safety of the medicine, how it works and how well it is tolerated. These clinical trials also identify preferred routes of administration (eg. tablet, liquid or injection) and help determine the appropriate doses for later studies. Phase I clinical trials are usually undertaken in centres appropriately equipped for the specialised monitoring and the high degree of surveillance needed.

- *Phase II* clinical trials are normally the first trials of the medicine in patients suffering from the condition for which the medicine is intended. The principal aim of these clinical trials is to determine effectiveness and safety. These clinical trials are undertaken in a small number of closely supervised patients and conducted by researchers regarded as specialists in the particular disease or condition and its treatment.
- *Phase III* clinical trials involve greater numbers of patients and are undertaken for the purpose of determining whether the medicine confers clinical benefit in the disease/s for which effectiveness was demonstrated in Phase II clinical trials. They also determine the nature and likelihood of any short term side effects. Phase III clinical trials are undertaken if the Phase II clinical trials indicate the medicine has potential benefit that outweighs the documented hazards.
- *Phase IV* clinical trials are those clinical trials undertaken after the medicine has been approved for the treatment of a particular disease. Phase IV clinical trials are undertaken to compare new medicines to a wider range of existing therapies. Such clinical surveillance are used to establish where, in the range of treatment options, the new medicine is best used.
(<http://www.medicinesaustralia.com.au/> accessed 11 Jan 2006)

Protocol Amendments

Within PaCCSC there are three categories of protocol amendments - minor, significant and major:

Minor

- minor changes in scheduling such as data collection points
- editorial changes to the protocol
- administrative changes to the protocol
- reduction of 10% or less in the intervention or control drug doses

These changes are usually made early in the study and do not require the approval of the Scientific Committee or the Trial Management Committee.

Minor amendments are instigated by site investigators or a member of the study investigator team. Amendments are approved by the study investigator team.

Minor amendments should be approved by the relevant Institutional Ethics Committee before implementation.

Document version changes will be at the 3rd point level, ie. V3.2.1 will become V3.2.2 if a minor amendment is made.

Significant

Significant amendments include:

- reduction in drug dose of more than 10%

- any increase in drug dose
- any change in scheduling that could increase toxicity
- any change in sample size or early closure criteria

All significant changes after the development phase of the protocol will require the approval of the Scientific Committee. Once significant amendments have been approved it is the responsibility of the coordinating investigator and National Manager to ensure that all investigators are notified.

Significant amendments should be approved by the relevant Institutional Ethics Committee before implementation.

Document version changes will be at the 2nd point level, ie. V3.2.1 will become V3.3.1 if a significant amendment is made.

Major

Major amendments include:

- addition of extra treatments and/or treatment arms
- changes in the study design
- changes in inclusion/exclusion criteria
- clear change in the intent of the study from that which was originally approved by the Management Advisory Board and Ethics committees.

These amendments cannot be made without the approval of the Scientific Committee. Once major amendments have been approved the protocol will be given a new version number.

Major amendments should be approved by the relevant Institutional Ethics Committee before implementation.

Document version changes will be at the 1st point level, ie. V3.2.1 will become V4.1.1 if a major amendment is made.

Procedure Responsibility

Scientific Committee

- to advise on protocol design
- approve any major amendments to study protocols

Coordinating investigator and Trial Management Committee

- oversee the development of the protocol for:
 - funding
 - study design
 - inclusion/exclusion criteria
 - analysis
 - reporting

- provide intellectual input into the design, authorship and planning of the protocol
- meet investigator group agreed deadlines for review and comment of the protocol.
- Approve minor and significant protocol amendments.

National Manager

- ensure that all investigators have the latest version for comment, review and input
- ensure that the latest version of the approved protocol is distributed for ethical approval and subsequent trial initiation
- coordinates the review and revision of the protocol within designated timeframes
- provide the most recent draft protocols and protocol changes to the Scientific Committee for review and comments.
- provide input and comment about the operationalisation of the protocol.
- ensure historical documentation of versions is maintained.

Site study coordinators

- report to National Manager
- discuss implementation of the protocol at that site with the Principal investigator
- ensures that any site specific plans required to implement the protocol are developed, recorded and reported to the Scientific Committee and the Trial Management Committee

Recording

All versions (electronic and paper) are kept within the study files. Documentation on amendments and variations to the protocol, including reasons for amendments is held within the latest version of the protocol.

Amendments

Amendments are variations to the study protocol after the protocol has been approved at the local sites, finalisation, ethics approval and implementation for the study protocol.

Amendments should be recorded providing:

- reason for the amendment
- the old text and amended text
- the date and number of the amendment

Amendment(s) should be attached to the study protocol to provide an ongoing record of the original and amended documentation.

All amendments should be distributed to all sites and the study sponsor within 1 week of the amendment acceptance as per the previous definitions.

Approval of New Protocols

A proposal synopsis (Attachment 1) should be forwarded to the PaCCSC Management Advisory Board (MAB) via the National Manager and the lead investigator at least one month prior to the meeting of the Management Advisory Board. The proposal will be assessed at the meeting, and if it is considered consistent with the directions of PaCCSC, a recommendation for the development of a draft protocol will be made.

The Scientific Committee will provide advice on study design and comment on the final protocol. A Trial Subcommittee will be formed by the Trial Management Committee to oversee further development and decide if external funding should be sought for the protocol or whether the protocol can be run within currently available resources.

The final protocol will be developed, circulated and signed off by all principal investigators at all sites. The trial will be registered with the Australian Clinical Trials Registry. This will be decided by the Scientific Committee.

Ethics approval will be sought at each participating site using the Ethics Template to complete the various requirements of the site IEC/HREC's. The study protocol is submitted in addition to the ethics submission form (if requested) as a separate document as the ethics submission form may not contain the protocol detail required.

Attachment 2 describes the protocol approval process.

Activation of Protocols

The final decision regarding the timing and method of protocol activation will be made by the Management Advisory Board and the trial coordinating investigator. This will be dependent upon:

- Scientific Committee and IEC/HREC approval; activation will commence in individual sites when ethics approval for that site is given.
- funding; if the study is to be externally funded, activation can occur once funding has been received, signed and all appropriate documentation completed.
- competition with other studies being conducted within individual sites; activation of studies may need to be staggered in order to minimise patient and staff associated burden.

Trial Registries listing.

The Australian Clinical Trials Registry.

The Australian Clinical Trials Registry (ACTR) is a national, online register of clinical trials being undertaken in Australia. The ACTR includes trials from the full spectrum of therapeutic areas of pharmaceuticals, surgical procedures, preventive measures, lifestyle, devices, treatment and rehabilitation strategies and complementary therapies. It has nationwide coverage of all clinical trials involving Australian researchers or Australian participants.

Proposal Synopsis

Title _____
Coordinating investigator _____

Institution: _____

Sponsor: _____

Protocol Number: _____

CTN required: Yes No
CTX required: Yes No

Collaborations: PaCCSC only
 Other trial groups, specify _____
 Pharmaceutical companies, specify _____

Rationale

Hypothesis (es) to be tested

Outcome measures

Population and setting

Objectives

Sample size

Study procedures and interventions

Statistical Analysis

Feasibility:

Economic Outcomes:

Sample Only

