PoCoG
Psycho-oncology Co-operative Research Group

Protocol Development and Approval

SOP ID: SOP_3.0.0-Protocol-120213

SOP development and approval

SOP developed by	Date	Associated document(s)
M Peate PoCoG Research Program Manager	04/01/2012	**SOP_3.3.1-Protocol-120104-Personnel Form Template**
M Peate PoCoG Research Program Manager	05/01/2011	**SOP_3.3.2-Protocol-120213-Protocol Template**
M Peate PoCoG Research Program Manager	04/01/2012	**SOP_3.3.3-Protocol-120104-CRF Template**
M Peate PoCoG Research Program Manager	25/09/2011	**SOP_3.3.4-Protocol-110925-AE_CRF Template**
M Peate PoCoG Research Program Manager	25/09/2011	**SOP_3.3.5-Protocol-110925-Responsibility Matrix**
M Peate PoCoG Research Program Manager	07/11/2011	**SOP_3.3.6-Protocol-111107-Protocol Checklist**
M Peate PoCoG Research Program Manager	05/01/2012	**SOP_3.3.7-Protocol-120105-AE Protocol Template**

Review panel: Melanie Bell, Haryana Dhillion, Monika Dzidowska, Danielle Miller, and Melanie Price.

Approved by	Date	Signature
Phyllis Butow PoCoG Executive Committee Chair	14/12/2011	
Monika Janda PoCoG Scientific Advisory Committee Deputy Chair	30/09/2011	

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SOP Revisions

Approved by:	Date	Signature (only required for PoCoG hard copy)	Description of change(s)

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Foreword

The Psycho-Oncology Cooperative Group (PoGoG) has developed a program of quality assurance for Psycho-Oncology Research. PoCoG's Quality System requires documentation of both management and procedural activities. This guidance document on Protocol Development provides a standard working tool that can be used to design a protocol for new research studies.

Questions regarding this document should be directed to:

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Please refer to www.pocog.org.au for the latest version of this and associated documents.

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Overview

Psycho-oncology Cooperative Research Group (PoCoG) endorsement requires studies to be scientifically justified and to contribute to improved scientific knowledge or improved patient outcomes. The development and implementation of a research study protocol are integral components of a rigorous study. Protocols need to comply with scientific and ethical standards. Regulatory authorities in Australia follow the good clinical practice guidelines issued by the International Conference on Harmonization (ICH) which standardises the format and content of protocols. A protocol describes the background, justification, objective(s), design, methodology, statistical considerations, organisation of the study, study duration, and a timeline on which the study is based. This includes the details of eligibility and informed consent, schedule of procedures including adverse event reporting, the calculation of results and reporting standards (including a detailed statistical analysis plan). A protocol provides a common reference document for study investigators, administrators, site staff and research staff, and details individual roles and responsibilities for the duration of the study. A study protocol enables the research to be undertaken at multiple sites, and/or by multiple people, in a consistent manner which complies with the study methods and requirements. It also provides a document that will enable other researchers to precisely replicate the study.

Purpose

A study protocol that meets scientific and ethical standards is a fundamental requirement of rigorous clinical investigations. The purpose of this standard operating procedure (SOP) is to describe the process of developing a study protocol in line with regulatory requirements.

Scope

This SOP is primarily designed to assist in the development of protocols for PoCoG studies. The SOP is relevant for all stages of the investigation and it is intended to be useful for all members of the research team involved in developing the study protocol, including:

- Principal investigator
- Project Development Manager (PDM)
- Study statistician
- PoCoG Director
- Research manager/ Study co-ordinator
- Members of the study management committee
- Research nurse/coordinator(s), research assistant, etc.
- Data manager(s)
- Quality assurance staff
- Support staff
- Independent Data safety monitoring committee

There are two types of PoCoG studies:

1. *PoCoG endorsed studies*

"PoCoG endorsed studies are those proposed in a well developed form by a PoCoG member or a collaborating group and submitted for endorsement to a PoCoG Scientific Advisory Committee (SAC) open meeting. Such projects may have widely differing levels of PoCoG involvement or support depending on the investigators' or groups' needs, ranging from scientific review only, to support in design and data analysis. Investigators also have the option to request that PoCoG fully administers a study on their behalf. If accepted, such study would become a PoCoG administered study."

2. *PoCoG administered studies*

"PoCoG administered studies are endorsed studies administered by PoCoG "in house". These may be developed through meetings such as a Concept Development Workshop a consensus workshop or as a result of a request for collaboration. PoCoG will propose and facilitate discussion of a topic and will facilitate further development of any research proposals which emerge. The composition of the writing

team (PI and CIs) will be based firstly on principles of intellectual property ownership, and secondly to maximise chances of grant success. We envisage that such studies will be seen as a collaborative group venture, to which many PoCoG members may have interest in contributing in terms of recruitment of patients, delivering an intervention and/or co-ordinating measurement of outcomes at their own centres. The project will be submitted through the PI's institution. If this is an institution other than PoCoG's administering institution (the University of Sydney), the PI will assist in making appropriate arrangements after the funding has been received to provide PoCoG with:

- Any necessary research and administrative agreements between the institutions
- A transfer of funds to PoCoG's administering institution to enable PoCoG to use the funds to administer the study."

The sections below outline the protocol development procedure for both types of studies except where indicated. It is strongly recommended that these procedures be applied to all studies, however it is recognised that this may not be practical for all types of psycho-oncology research or for all endorsed studies.

Guiding Principles

Good clinical research practice

Good clinical research practice conducts studies in accordance with the principles outlined in the following sources:

- International Conference on Harmonisation documentation on Good Clinical Practice (ICH-GCP, http://www.ich.org/home.html) and the Therapeutic Goods Administration (TGA) annotated version (http://www.tga.gov.au/industry/clinical-trials-note-ich13595.htm)
- the National Health and Medical Research Council National Statement on Ethical Conduct in Human Research (henceforth referred to as the 'national statement') http://www.nhmrc.gov.au/publications/synopses/e35syn.htm)
- The Australian Code for the Responsible Conduct of Research (http://www.nhmrc.gov.au/publications/synopses/r39syn.htm)
- Therapeutic Goods Administration's Australian Clinical Trial Handbook (http://www.tga.gov.au/industry/clinical-trials-handbook.htm)
- Declaration of Helsinki (http://www.wma.net/en/30publications/10policies/b3/index.html)
- National Cancer Institute Common Terminology Criteria for Adverse Events (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm)
- CONSORT statement (http://www.consort-statement.org/home/)
- STROBE statement (http://www.strobe-statement.org/)
- Other guidelines as applicable (http://www.pocog.org.au/content.aspx?page=studyobligations)

Privacy and Confidentiality

PoCoG endorsed studies must have procedures in place to ensure that the conduct of researchers and staff involved are in accordance with Australian federal, state and international privacy legislation. Participant confidentiality must be maintained at all times except as required by law. Study protocols and other information are often confidential and should not be provided to personnel not involved with a study.

Ethics

PoCoG research studies must be designed to ensure the safety and health of research participants and to answer specific research questions. These details need to be provided in the study protocol. All PoCoG endorsed studies must have the relevant ethical, governance and regulatory approvals prior to opening the study for recruitment.

Registration

PoCoG requires all newly endorsed research studies to register with a recognised Clinical Trials registry (e.g. Australian New Zealand Clinical Trials Register: http://www.anzctr.org.au/) prior to seeking ethics approval. The Clinical Trials Registration Number (CTRN) should be listed on the protocol.

Definitions and Abbreviations

Adverse Event (AE)	Any untoward occurrence in a study participant administered an intervention. An AE can therefore be any unfavourable and unintended sign, symptom, or disease temporally associated with the use of an intervention, whether or not related to the intervention
Analytical study	A method for testing a hypothesised association between possible causes of the outcome (disease) and a outcome (disease).
Audit	A quality control procedure reviewing or evaluating study processes to assess compliance with the study protocol and procedures.
Case control study	An epidemiological study design comparing people with a disease (‘cases’) to people without the disease ('controls'), typically match on characteristics such as age and gender. Data on “exposure” prior to disease onset are collected retrospectively and the groups are compared.
Chief Investigator (CI)	A Chief Investigator (CI) is involved in the study design, grant applications, research protocol development and is a member of the *Trial/ Study Management Committee*.
Clinical Trial/Study	A study in humans investigating some aspect of an intervention. This may include ascertaining safety, feasibility, and/or efficacy, as well as to identify, verify and/or measure the effects, and/or adverse reactions.
Cohort	A group of people who share a common characteristic or experience within a defined period.
Cohort study	A longitudinal study following a group of individuals over time to determine the natural history of a disease/outcome.
Controlled study	A study allocating participants to an intervention or control/usual care.
Coordinating centre	The site which the study is coordinated, usually the site where the Principal Investigator is based and where funding is administered.
Cross-sectional study/analysis	The observation of a population, or a representative subset, at a defined time, often used to assess prevalence of acute or chronic conditions.
Descriptive/ ecological study	An epidemiological study in which the unit of analysis is a population rather than an individual and describes characteristics of the population or disease.
Direct equity	Any ownership interest, stock options, or other financial interest whose value cannot be readily determined through reference to public prices, or any equity interest in a publicly traded corporation. Direct equity needs to be declared prior to study commencement and up to, and including, one year following study completion.
Human Research Ethics Committee (HREC)	Human Research Ethics Committees responsible for the ethical review of research studies involving humans
Hypothesis	A tentative explanation for an observation, phenomenon, or scientific “problem” which generally can be answered with a yes or no response.
Interventional study	A study involving an intervention to some or all of the participants.
Non-randomised (quasi-experimental) study	A study which does not randomly allocate participants into groups and therefore does not control participant allocation to the treatment, intervention or other factors being investigated.
Observational study	A study which examines prevalence or draws inferences about the possible effect of a treatment or risk factor(s) on participants and does not control participant allocation into groups.
Principal Investigator	The investigator responsible for the co-ordination of Chief Investigators and

(PI)	Site Investigators in a multicentre study. Often the Principal Investigator is also Chief Investigator A (CIA) on grant and ethics applications and will lead the *Management Committee*. Also: Coordinating Investigator.
Project Development Manager (PDM)	The person who will be principally responsible for the development and/or management of a study.
Protocol	A protocol describes the background, justification, objective(s), design, methodology, statistical considerations, organisation of the study, study duration, and a timeline on which the study is based. This includes the details of eligibility and informed consent, schedule of procedures including adverse event reporting, the calculation of results and reporting standards (including a detailed statistical analysis plan). A protocol provides a common reference document for study investigators, administrators and site staff, detailing individual duties and responsibilities throughout the duration of the study. A protocol enables the research to be undertaken at multiple recruitment sites in a consistent manner which complies with the study methods and requirements. This also provides a document that will enable other researchers to precisely replicate the study.
Quality Assurance (QA)	A set of preventative activities which focus on study processes. These include the planned and systematic actions established to ensure that the study is performed and the data are generated, documented (recorded), and reported in compliance with Good Clinical Practice (GCP) and the applicable regulatory requirement(s).
Quality Control (QC)	Detection activities which focus on detecting 'problems' with research study processes. The operational techniques and activities undertaken within the Quality Assurance (QA) system assess whether the requirements for quality of the study-related activities have been fulfilled.
Randomised Controlled Trial (RCT)	A study involving participants who are randomised to receive the intervention or control/usual care.
Scientific Advisory Committee (SAC)	A group of individuals who have been assembled to offer advice on the scientific quality of studies.
Serious Adverse Event (SAE)	Any event that suggests a significant hazard, contraindication, side effect, or precaution, that may jeopardize the patient, whether or not it is considered to be associated with the intervention, is a SAE.
Site Investigator (SI)	The person responsible for the conduct of the research study at a study recruitment site. The Site Investigator (SI) may also be responsible for the clinical care of the patient. If a study is conducted by a team of individuals at a study site, the SI is the leader of the team. *NOTE: in psycho-oncology non-intervention studies, the clinical care of the patient remains with the treatment team while the PI retains responsibility for the study at the site.*
Standard Operating Procedures (SOPs)	Detailed written instructions designed to achieve uniformity of the performance of a specific function.
Study Management Committee (SMC)	A committee composed of the PI and CIs who manage the trial. The SMC usually also includes a statistician, project manager/ study coordinator, representatives of the various disciplines involved in the trial, and consumer representatives. Also known as the Trial Management Committee (TMC).
Uncontrolled study	A study where all participants receive the intervention and are followed for a certain amount of time without a comparison (control) group.

Qualifications and Responsibilities

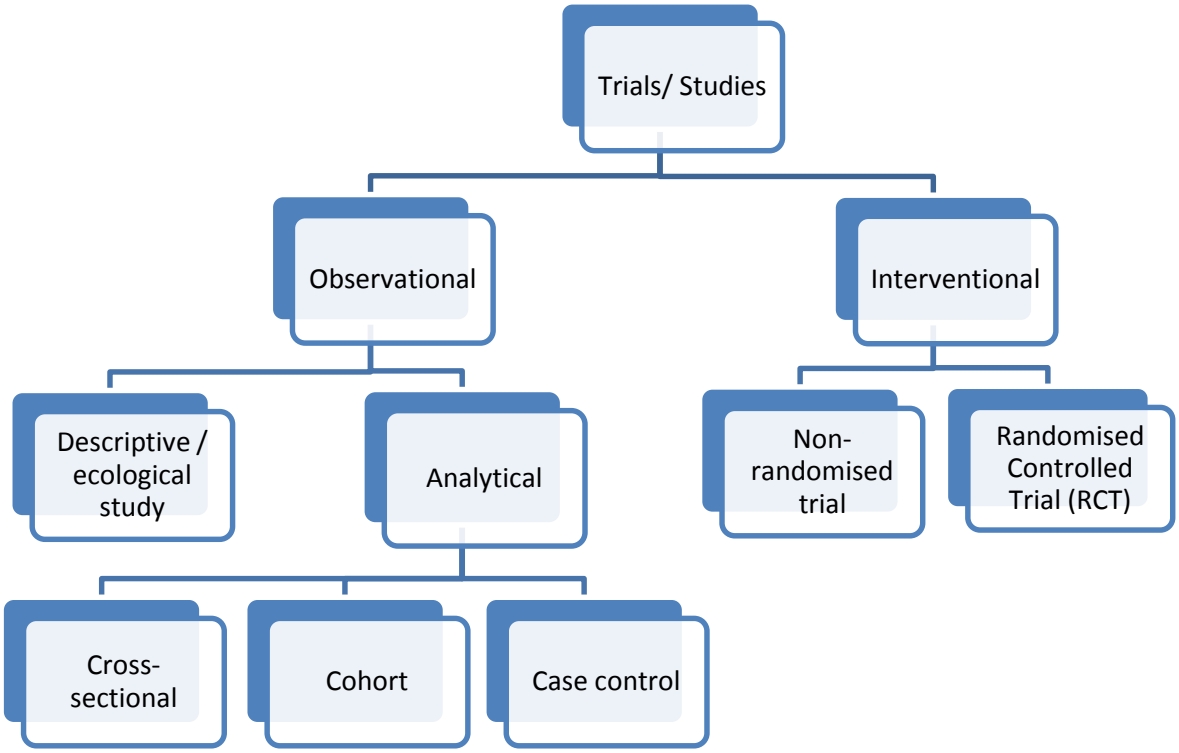
The Principal Investigator (PI) is responsible for the development of the study protocol, but should involve the Study Management Committee (SMC) (see SOP 2.0.0 establishing a SMC). The Protocol Development Responsibility Matrix (SOP 3.3.5) details the specific responsibilities of the SMC members in

developing the study protocol. All members of the SMC should be qualified by education, training and experience to assume responsibility for the proper conduct of the study.

1. Procedure

While psycho-oncology employs a variety of research designs (see Figure 1), depending on the research question, the rigour used for standard medical intervention trials is applicable to psychosocial and supportive care research. This includes the development of a thorough protocol detailing all aspects of a clinical trial.

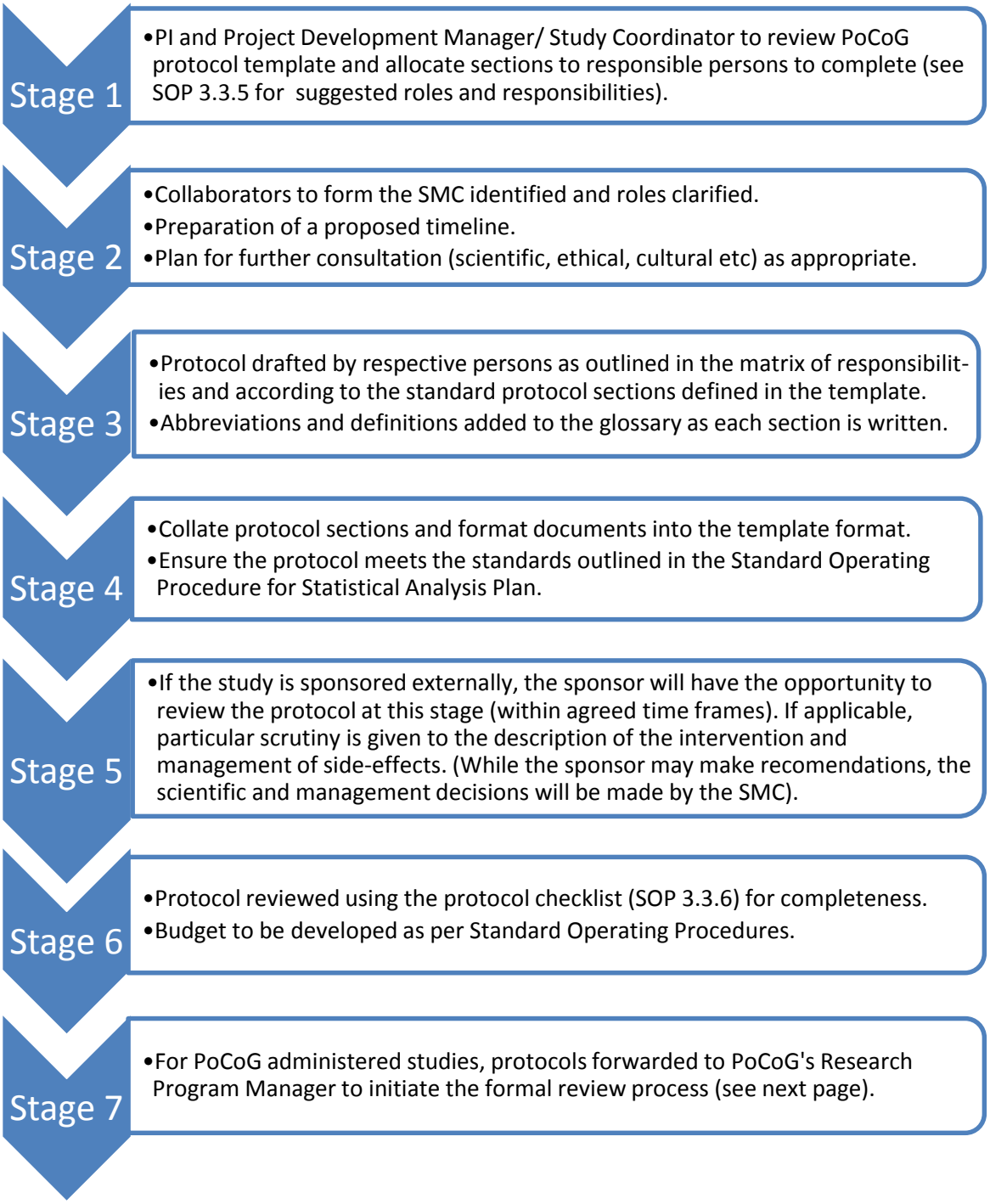
Figure 1: Types of research studies. For descriptions of these types of studies please refer to the definitions and abbreviations section of this document. Adapted from http://www.fogsi.org/fundamental_clinical_research.html



The protocol should be based upon the content of the proposal endorsed by the PoCoG Scientific Advisory Committee (SAC) and designed in line with recognised standards of protocol content, format and usability. The contents of a protocol should generally include the topics outlined in the PoCoG template (see SOP 3.3.2), while recognising that site and study specific differences may require modification of this general protocol format. The protocol template is designed for use in both interventional and non-intervention study designs, and therefore, flexible. ***The text in "<>" provides guidance for the content of each section and examples are also provided.*** The content should be clearly set out, internally consistent and conform to SOPs and applicable regulatory requirements. Care must be taken with use of abbreviations, units for parameters, references, spelling, and grammar. The development of the protocol should be approached from the perspective that this document alone will enable replication of the study.

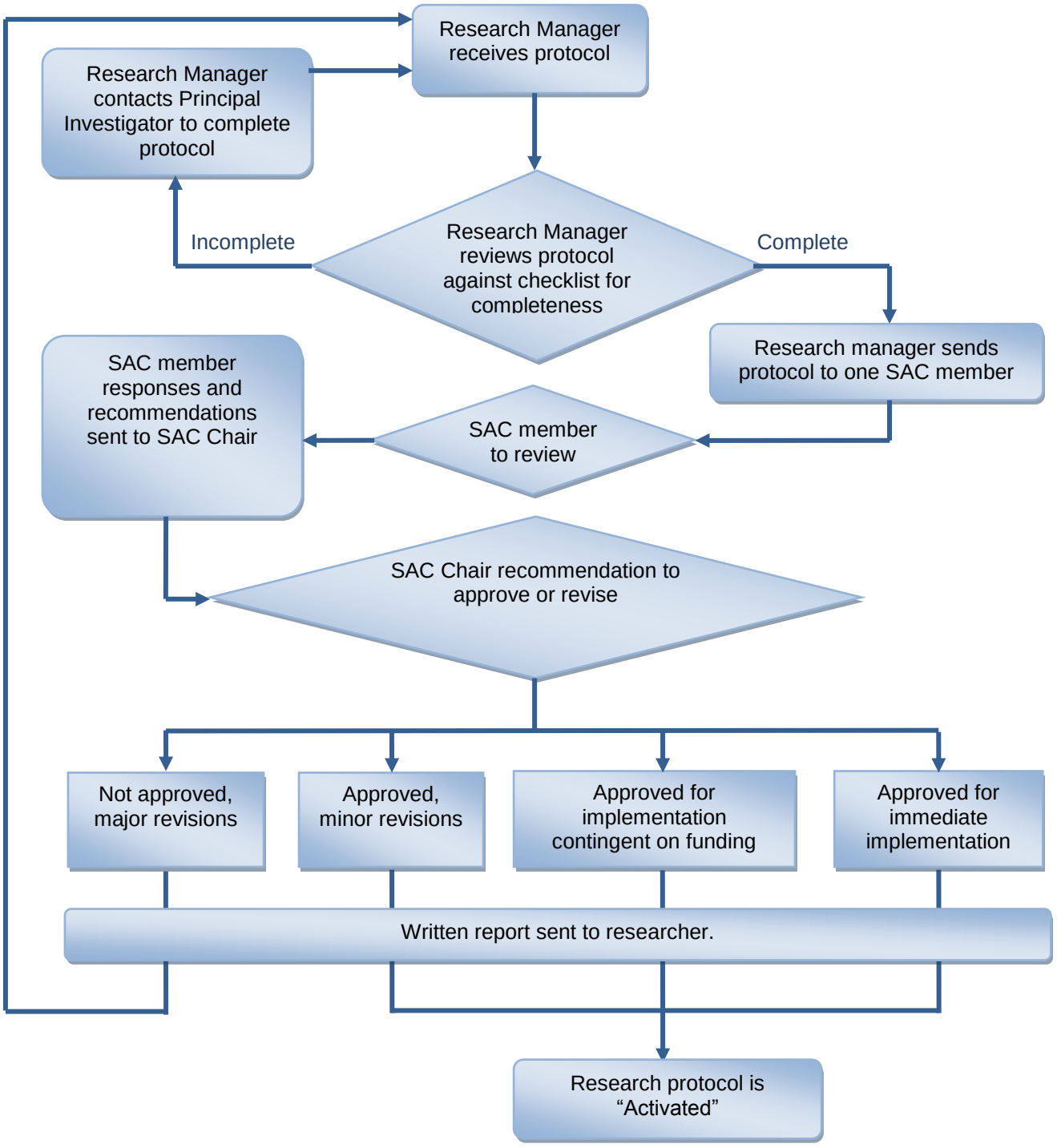
The process of developing a protocol is shown in Figure 2.

Figure 2: Stages of research protocol development



The protocol and accompanying documents (including SMC personnel form, ethics and/or funding information listed below) should be submitted to the Research Program Manager to undergo for SAC review and approval (the process is outlined in Figure 3). Study activation may commence once the protocol has been approved and copies of relevant approvals from other bodies, such as ethics, have been submitted to PoCoG.

Figure 3: Protocol Review Process



1.1. Intergroup studies

Intergroup collaborative studies where PoCoG is the junior partner, the study protocol still needs review and approval from the PoCoG SAC to ensure that PoCoG requirements are met and to ensure the protocol is acceptable from a psycho-oncology perspective. A written agreement outlining the division of responsibilities between PoCoG and the Collaborative Group is essential.

1.2. Industry partner studies

In studies involving an industry partner, the protocol needs to meet all PoCoG requirements as per intergroup collaborations. This includes the protocol being review and approved by the PoCoG SAC to ensure that PoCoG requirements are met and to ensure the protocol is acceptable from a psycho-oncology

perspective. A written agreement outlining the division of responsibilities between PoCoG and the industry partner is essential.

2. Records management

2.1. Protocol management

It should be ensured that all protocols meet PoCoG requirements as outlined in PoCoG's SOPs. Protocols in development should use a "draft" watermark. All protocols should include a date of the current version and the PoCoG endorsement number (allocated by PoCoG) on each page in the footer. Amended protocols should include the amendment number and date in the footer.

2.2. Amendments to protocols

In the event that an amendment of a PoCoG protocol is required, a summary of amendments should be submitted to the SAC for approval prior to submission to the HREC. The timing for these amendments should reflect the importance of the change. Table 1 provides a guideline for the timing of submitting an amendment.

Table 1: Type of protocol amendments

Amendment type	Definition	Example	PoCoG Notification
Relates to safety	Anything that requires immediate implementation to ensure patient safety	Intervention results in an unexpected SAE	***Notification as soon as possible.*** A modified version of the protocol, with the amended and dated protocol version clearly marked on the cover page, and accompanied by a letter of explaining the rationale for the amendment. A copy of the HREC approval must also be provided to PoCoG.
Major amendment	Anything that requires a change in the delivery of the intervention, eligibility criterion, recruitment process	Change in recruitment process.	***Approval required.*** A modified version of the protocol, with the amended and dated protocol version clearly marked on the cover page, and accompanied by a letter explaining the rationale for the amendment.
Minor amendment	Administrative changes that do not change the research plan or the intent of the study	Change of site investigator details	***Notification not required.*** For some minor amendments it will be appropriate to notify PoCoG by way of the biannual reports.

2.3. Ethical requirements for continued endorsements

Current ethical approval for all PoCoG studies is a requirement for continued endorsement. A list of HREC approval numbers and dates for each site should be provided to PoCoG and copies of the approval letters submitted to PoCoG on request. PoCoG requires information about the Adverse Events (AEs) and whether these have been addressed in the semi-annual study report. The HRECs should be advised that as sponsor representatives, the PoCoG Executive Director and Research Manager, may require access to the data on request.

2.4. Funding information

PoCoG needs to be appraised of the funding details for a study and an assessment of the viability of completing a PoCoG endorsed study with this budget. For PoCoG administered studies, a budget plan for the lifetime of the study needs to be developed and submitted to the Executive Office. PIs are encouraged to seek assistance from the Executive Director in creating the budget and including the Executive Director in regular reviews and modification (if required) of the budget.

3. Quality Assurance (QA) – templates, forms and checklists

PoCoG is responsible for Quality Assurance (QA) for endorsed studies, and requires that Quality Control (QC) procedures are embedded in study protocols as a core component of QA. The QC procedures are designed to allow the self-verification of the consistency and quality of the research (such as self-checks or recounting). The PI and SMT need to ensure that they include appropriate QC procedures within the study protocol and ensure that they are consistently applied place prior to commencing the study. Specific criteria for each process should be included, including the frequency of checks and rationale for inclusion or decision to be made. There should be clear limits to the QC data and documentation for the actions required should the QC data not meet minimum requirements (i.e. appropriate monitoring and stopping rules). To assist with QA PoCoG have developed a number of templates, forms and checklists outlined below.

3.1. Template: Study Management Committee (SMC) Personnel Form

The purpose of a Personnel Form Template (SOP_3.3.1) is to provide a consistent documentation of all of the people involved in a study, their qualifications, contact details and their roles and responsibilities for the study. PoCoG is to be notified of any changes or additions to this list in the biannual progress report.

3.2. Template: Protocol

Different research studies will have different requirements as to content of a protocol. The purpose of the Protocol Template (SOP_3.3.2) is to guide the developing the study protocol. Utilising the template document acts as a prompt for considering which sections and what information is relevant for a study (some sections may not be relevant to all studies). While PoCoG administered studies are required to use the template when developing a protocol, the template is meant to be flexible. Throughout the template, the bracketed (“<>”) text provides guidance for the content of each section and the orange text provides an example.

3.3. Template: Recruitment Case Report Form (CRF)

The purpose of the Recruitment Case Report Form template (SOP_3.3.3) is to assist in providing recruitment sites with a consistent method of documenting information about potential participants (or ‘cases’) and forwarding this information to the coordinating centre. This may include name and contact details, whether consent has been given, and any other details needed for recruitment of participants into a specific study. The PoCoG template is to be used as the basis for the CRFs for administered studies.

3.4. Template: Adverse Events Case Report Form (AE-CRF)

The purpose of the Adverse Event Case Report Form (AE-CRF, SOP_3.3.4) is to assist in providing sites with a consistent format and information to be documented in the event of an Adverse Event (AE). This report format is designed as a stand-alone document that can be sent to the coordinating centre and ethics committee. The PoCoG template is to be used as the basis for the CRFs for administered studies. All studies, even low risk studies, are advised to have an AE system in place.

3.5. Template: Protocol development responsibility matrix

The purpose of the Responsibility Matrix (SOP_3.3.5) is to guide the documentation the specific details of the positions and roles responsible for development of each section of a protocol. The roles should be delegated by the PI.

3.6. Checklist: Protocol content

The purpose of the Protocol Checklist (SOP_3.3.6) is to provide a simple means of ensuring all aspects of the protocol has been comprehensively detailed prior to submission of the formal protocol for PoCoG approval. The form should be completed by the person primarily responsible for the preparation of the protocol, such as the PI, a CI or the Project Development Manager.

3.7. Checklist: AE Protocol template

The purpose of this template (SOP_3.3.7) is to describe the process for managing Adverse Events and should be an attachment to the study protocol.

4. References

http://www.cancerinstitute.org.au/research-grants-and-funding/clinical-trials/quality-assurance-program

http://www.jcto.co.uk/SOP/gcpProtocolSOP.html

http://www.tga.gov.au/industry/clinical-trials-note-ich13595.htm