

If you intend to submit a clinical trial synopsis/research proposal for review and consideration please complete this form. The Executive Committee will review this proposal and relevant feedback will be provided as soon as possible.

Please forward all queries and the completed synopsis to the following email:
anzmtg@usyd.edu.au

CLINICAL TRIAL PROTOCOL SYNOPSIS/RESEARCH PROPOSAL OUTLINE

Lead Investigators and/or groups
Title
Brief Background and rationale
Aim
Objectives
Hypotheses
Population and setting
Interventions (if applicable)

Outcomes and measures Primary outcome: Secondary Outcomes:
Study Design and Procedure – outline only
Statistical considerations/sample size/data collection
Timeline
External/Internal Funding sources
Feasibility/ Recruitment
Request for resources from the ANZMTG
Do you wish to apply for funding assistance to conduct this study/trial?
Will you require project management assistance with this study/trial?
Will you require data collection or data management assistance during this study?
Will you require biostatistical advice or analysis conducting during this study?

Developing an outline for a research proposal/clinical trial

Introduction

An *outline* is a preliminary account of the plan for a project. The purpose of an outline is to provide a brief, clear summary that helps readers understand, discuss, refine and support (hopefully) a proposed study or trial.

Standard headings provide a useful structure and starting point for an outline proposal. These headings help the writer to include what is important and the reader to find it. Readers of an outline are appraising the proposed study. Typical criteria include the importance of the problem, the potential impact of the intervention, scientific excellence and feasibility. Innovativeness and alignment with particular priorities may also be relevant.

An outline also provides a useful basis for writing a protocol. The protocol will cover everything in the outline, much of it in more detail. In practice, the outline and protocol are often written together and although this is sensible, it sometimes results in an outline with too much detail. An outline should only give readers the information they need *to decide whether to support* the study (up to two pages). The information needed *to do* the study should be left to the protocol.

Lead Investigators and groups

List the individuals and groups who have contributed to the proposal and agreed to support it. If a collaborative group has been involved, indicate its current level of commitment: e.g. submitted for review by Scientific Advisory Committee (SAC), approved by SAC, presented at group meeting, agreement to take on if funded, agreement to take on and obtain funding.

Title

The title should briefly and accurately describe the study design and the 3 components of a 'well-built clinical question' advocated by proponents of evidence-based medicine. Study design is the most important criterion for determining the validity of a study. The 3 components of a well-built clinical question are the population, interventions, and outcomes. Each of these elements is discussed in more detail below. The title should also indicate that the document is a proposal.

Brief Background and Rationale

This section of the outline should cover the extent and scope of the clinical problem (why the area is worth researching), the rationale for the interventions (if applicable), and the rationale for the study. Evidence supporting the importance of the problem is important. What is known about available interventions should also be summarized, along with possible areas for improvement. This naturally leads to the rationales for the experimental and comparator treatments. Listing the potential pros and cons of the study interventions (if applicable) may highlight the importance of doing, say, a randomized trial. If so, how the trial will improve knowledge and practice should also be described.

Aims, Objectives and Hypotheses

The *aim* of a study describes the overall goal of the research in general terms, whereas the *objectives* define the specific aspects to be determined. There should be a single, primary objective. *Hypotheses* are the specific predictions a study is designed to test. The progression of logic through these headings is usually listed as Aim → Objective → Hypotheses.

Population and Setting

The target population and setting should be described briefly, along with the most important inclusion and exclusion criteria. The target population defines the group suitable for the intervention, if applicable. The setting defines the environment in which subjects will be recruited and treated. The inclusion and exclusion criteria specify the sort of people that may

and may not participate in a research study or trial. An accurate description of the population and setting helps reviewers determine the generalizability and applicability of a study.

Interventions (if applicable)

This section of the outline describes the nature of the interventions and how they will be administered. For drugs, this includes dose, titration, duration, modifications for toxicity, allowed and prohibited concomitants, and rescue interventions. *Placebos, active controls* and *non-drug interventions* should also be outlined in sufficient detail for reviewers to understand what they will involve. If *best supportive care* is to be used as a control arm, then its nature and details should be described.

Outcomes and Measures

This section of the outline summarizes the effects of interest and how they will be measured, quantified and compared. It is useful to distinguish between outcomes, outcome measures, endpoints, and measures of effect when designing and planning a study. However, these terms are frequently used loosely and interchangeably so a flexible approach is necessary.

Outcomes are the consequences of interest that may occur in response to an intervention. There are usually many outcomes of interest in a clinical trial, but the larger the number of outcomes tested, the greater the likelihood of spurious results. The outline should distinguish a single *primary outcome* from the remaining secondary and tertiary outcomes. A positive result on a single primary outcome selected before the data are examined provides much stronger support than a similar result selected from a multitude of outcomes after they have been tested.

The **primary outcome** should be the most important and compelling one: the outcome you would (and should) choose to believe if there are conflicting results. The primary outcome for the trial should correspond with the primary objective and primary hypothesis; it should also be the basis for the sample size calculations.

Outcome measures are the tools used to quantify the outcome of interest, for example RECIST criteria for measuring objective tumour response, or a numeric rating scale for pain intensity. *Validity* is the extent to which an instrument measures what it is supposed to measure. Strictly speaking, the term '*endpoint*' refers to health events or observations that lead to completion or termination of follow-up of an individual in a study. These can include positive or negative effects of the treatment, disease, or other factors. Death, relief of symptoms, withdrawal from treatment, and particular adverse events are examples of endpoints. However, the term endpoint is often used to denote the observation or summary statistic used to express the overall effect of a treatment. The specific endpoints should be mentioned in the study's objectives.

Study Design and Procedure

One sentence is usually sufficient to summarize the important aspects of a research study's design. However, brevity belies the importance study design, which is the most important aspect for determining the validity of a study. These aspects and the commonly used designs are described below.

The purpose of a clinical trial is to answer specific questions about the effects of a treatment. The design of a trial determines what sorts of question it is able to answer. The first methodological question reviewers ask is whether the study design is suitable for answering the study question. Phase 1 and 2 trials are designed to guide research. Phase 1 trials are about feasibility. Phase 2 trials are about activity and toxicity. Phase 3 trials are designed to guide clinical practice and are about benefits and harms for patients.

This section of the outline should also summarize how subjects are recruited and followed. One approach is to describe what happens to subjects, another is to summarize the schedule of study assessments from the protocol. The trick is to provide a broad outline and avoid excessive detail. The outline should briefly describe what important things happen when; the details belong in the protocol. The *timing* of assessments is important. Assessments should be

frequent enough to detect important changes, but not so frequent that they annoy participants. Assessments should continue long enough to detect important changes, but not so long that extraneous factors obscure the treatment effects. It is worth considering whether the study aim is to determine if a treatment works or how long it works. If patients are taken off a study because of worsening condition, then it is important to include their ratings at the end of study visit, otherwise the results will give a falsely optimistic view of their experience.

Statistical Considerations/sample size/data collection and analysis plan

This section of the outline should include the sample size, analysis plan, study duration and tactics for dealing with multiple outcomes, missing data, and attrition. Simple, valid methods are available for the vast majority of questions. Early involvement of an experienced statistician is vital.

The sentence on sample size should specify the number of subjects and endpoints needed to detect the minimum clinically important effect with a specified test, level of confidence, significance and power. The key decision is how small an effect would warrant declaring the results 'clinically significant'.

The analysis plan should specify analyses that are by 'intention to treat' and justify those that are not. Cancer research studies always include multiple outcomes, attrition and missing data; all of which increase the risk of spurious results. The analysis plan should specify methods for dealing with these problems.

Timeline and Funding sources

The outline of the study should include a realistic timeline and arrangements for funding any resources you may require. Remember to take all aspects of conducting the study into consideration.

Feasibility/Recruitment

Feasibility, especially of recruitment, is a key consideration for reviewers of a concept outline. This section should outline the proposed sources of patients and estimated recruitment rates. If the success of the study depends on getting treatments, reagents or other materials, then this should also be briefly addressed.

Request for resources

As a member of the ANZMTG, this form enables you to submit a request for resources to support your research proposal or trial through the ANZMTG Executive Committee, possibly in combination with other sources of funding (industry, local, state, national and international bodies etc)