# Developing a concept outline for a proposed clinical trial

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 a proposed study. The key readers of an outline for a proposed trial are potential investigators and peer-reviewers, for example: members of scientific advisory boards, grant review committees and institutional and review boards. These readers are usually knowledgable, busy and trying to answer three basic questions about a proposed study:

1. What makes this proposal interesting or unique? (that is, what is the potential benefit for clinical practice?)
2. Should we support it?
3. Should it be changed?

An outline should quickly and clearly convey the information they need to answer these questions.

Standard headings provide a useful structure and starting point for an outline. 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. Innovation and alignment with particular priorities may also be relevant.

An outline is also 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 give readers only the information they need to decide whether to support the study. The information needed to do the study should be left to the protocol.

One page is the ideal length for a concept outline. Use both sides if you must.

### 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, the interventions, and the outcomes. The title should also indicate that the document is a proposal.

### 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, and the rationale for the trial. Evidence supporting the importance of the problem is important. What is known about available interventions should also be summarised, 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 highlights the importance of doing a randomised trial. 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.

### Study design

One sentence is usually sufficient to summarise the trial's design. It should cover the phase, blinding, and any other distinctive features of trial design. However, brevity belies the importance of 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 sort of question it is able to answer. The first methodological question reviewers ask is whether the study design is suitable

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for answering the study question. Phase I and phase II trials are designed to guide research. Phase I trials are about feasibility. Phase II trials are about activity and toxicity. Phase III trials are designed to guide clinical practice and are about benefits and harm for patients.

### 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. 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 trial. An accurate description of the population and setting helps reviewers determine the generalisability and applicability of a study.

### Interventions

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 nondrug 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 summarises 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 procedures

This section of the outline should 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. It should account for the likely trajectory of the disease and its consequences with and without treatment.

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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**

This section of the outline should briefly describe 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.

**Feasibility**

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.

**Competing studies**

Investigators should demonstrate that they have looked for ongoing or planned trials in this area. If similar studies are being done or planned, then brief details should be included to highlight important similarities to, and differences from, the proposed trial.

**Funding and support**

All trials need funding. Investigators should consider possible sources of funding that may be appropriate for their proposed trial (eg. industry; local, state, national and international granting bodies; and, other sources).

**Investigators and groups**

List the individuals and groups who have contributed to the concept and agreed to support it. If a collaborative group has been involved, indicate its current level of commitment: eg 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.

Contact the Outreach team (trials@ctc.usyd.edu.au) or through the website (www.clinicaltrialsoutreach.org.au) for further advice on this topic.

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**Trial concept outline: insert details below the headings (2 pages or more, font size at least 10 pt please)**

| | |
|---|---|
| **Title** | |
| **Background and rationale** | Significance and innovation |
| **Aim** | Scientific excellence |
| **Objectives** | |
| **Hypotheses** | |
| **Population and setting** | |
| **Interventions** | |
| **Study design** | |
| **Outcomes and measures** | |
| **Study procedures** | |
| **Statistical considerations** | |
| **Feasibility** | Aspect of scientific excellence but often overlooked. Review. |

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| | |
|---|---|
| **Competing studies** | |
| **Funding and support** | |
| **Investigators and groups** | Team capacity and track record |

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