

A guide to developing concept outlines for proposed studies

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Introduction

The aim of this guide is to help clinical researchers turn good ideas into successful research projects by providing a framework and instructions for writing a standardised concept outline for a proposed study.

A *concept outline* is a preliminary account of the plan for a project. The purpose of a concept outline is to provide a brief, clear summary that helps readers understand, discuss, refine, and (we hope) support a proposed study. The key readers of a concept outline for a proposed study are potential collaborators and peer-reviewers, for example: members of scientific advisory, grant review, and institutional review boards and committees. These readers are usually knowledgeable, busy, and trying to answer two basic questions about a proposed study: “Should we support it?” and “Should it be changed?” A concept 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. They help the writer to include what is important, and the reader to find it. Readers of a concept outline are appraising the proposed study. Typical criteria for the appraisal of a study include the importance of the problem; the rationale for, and potential impact of, the proposed intervention(s); and, the scientific excellence and feasibility of the proposed research. Innovativeness and alignment with specific priorities may also be relevant.

A concept outline also provides a useful basis for writing a study synopsis and a study protocol. The study protocol is the instruction manual for how a study is conducted, and it covers almost everything that is in the concept outline in finer detail. The study synopsis will also include much of what is in the concept outline, but summarises what is done, not what is proposed. In practice, the concept outline, synopsis, and protocol are written and modified together, and although this is sensible, it often results in outlines (and synopses) that are too long and detailed. A concept outline should give readers only the information needed for *deciding whether to support* a study. The information needed for *doing* a study should be left to the protocol.

One page (A4) is the ideal length for a concept outline. Use both sides if you must.

1. 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 key components of a well-built clinical question are the population, intervention(s), and main outcome. Each of these elements is discussed in more detail below. The title should also indicate that (if) the document is a proposal.

2. Background and rationale

The background is the important information needed to understand the study that is being proposed. The rationale is the set of reasons that make it logical to do the study in the way it is proposed. 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 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 rationale(s) for the experimental treatment (and comparator). Listing the potential pros and cons of the experimental and comparator interventions highlights the importance of doing a randomised trial (if this is what is proposed). The more briefly this can be done, the better. How the study will improve knowledge and practice, in other words, what difference the results of the study will make, belongs in the section 11, significance.

The optimal length of the background and rationale for a concept outline is a few lines (1 or 2 sentences) if you envisage using one side of the page, or a paragraph (4 or 5 sentences) if you envisage using both sides of the page. Several pages of background, rationale, and references will be needed for a ‘letter of intent’ to industry or a grant application to a funding body. It is good practice to write this longer version early in the development of a research proposal, and definitely circulating your study proposal for consideration by others.

3. Aims, objectives and hypotheses

Aims are general. Objectives are specific. The *aims* define the nature and scope of a study by describing what it will determine in general terms. For most clinical trials, the aim is to determine one or two of the following: safety, feasibility, activity, and benefits. The *objectives* define what a study will determine in more precise terms, by specifying the endpoints or measures of effect corresponding to the general aims. There should be a single, primary objective corresponding to the primary aim of the study. All other objectives are secondary or tertiary. Secondary objectives are about other endpoints that are interesting, but not the primary focus of the study, typically other aspects of safety, activity or benefit. Tertiary objectives are about additional questions that a study will address, often regarding associations and interactions between baseline characteristics, study interventions, and study endpoints. Tertiary objectives are often exploratory, descriptive and hypothesis-raising rather than hypothesis-testing.

Hypotheses are the specific predictions a study is designed to test. The primary objective and key secondary objectives should each have a corresponding hypothesis including the same endpoint or measure of effect. The primary hypothesis should be quantitative and is the basis of the sample size justification. Correlative and/or exploratory aspects of an intervention study are usually best incorporated as tertiary objectives.

4. Study Design

One sentence is usually sufficient to summarize the important aspects of a study'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. 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 determine feasibility and safety to indicate whether further research is possible. Phase 2 trials aim to determine activity and safety to indicate whether further research is worthwhile. Phase 3 trials are designed to guide clinical practice by determining effects on direct measures of benefits and harms to patients to indicate whether an intervention should be adopted in practice.

5. 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 characteristics of people who may and may not participate in a study. An accurate description helps reviewers judge a study's generalisability and applicability.

6. Intervention(s) or Exposure(s)

Interventions are actions taken to improve a condition or situation. Their nature and how they will be administered should be briefly described here. For drugs, this includes dose(s), duration(s), important 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, then its nature and details should be described briefly.

For observational studies, we talk about exposure(s) and comparison groups.

7. Outcomes, measures and endpoints

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 examined, the greater the likelihood of spurious findings. *Outcome measures* are the tools used to quantify the outcome of interest, for example RECIST criteria for objective tumour response, or a numeric rating scale for pain intensity. A *validated* outcome measure is one that has been shown to reliably measure what it is supposed to measure.

Strictly speaking, the term '*endpoint*' refers to a health event or observation that leads to the completion or termination of follow-up for an individual in a study. These can include positive or negative effects of treatment, disease, or other factors. Death, relief of symptoms, withdrawal of treatment, a specific adverse event, or a specified time point are examples. However, it is probably better to use *endpoint* to denote *the observation or summary statistic* used to express the overall effect of a treatment on an individual. The term *measure of effect*

refers to how groups of individuals will be summarized (and compared), for example response rate (difference), progression free survival distribution (hazard ratio, logrank test).

A positive finding on the single primary outcome, measure, endpoint, measure of effect, objective and hypothesis, all selected before the data were examined, provides much stronger support than the same finding selected from a multitude after they were examined. The primary outcome (endpoint) should be the most important and compelling one: the outcome (endpoint) you would (and should) choose to believe if there are conflicting results. The primary outcome, measure, endpoint, measure of effect, objective and hypothesis should correspond with one another, and should be the basis of the sample size calculations.

If a study's endpoints are clearly incorporated in its objectives, then this section can be used to include important details of assessment methods, measurement scales, definitions.

8. Study Procedures

This section should briefly summarize how subjects are recruited and followed. One approach is to describe what happens to subjects, another is to summarize the *schedule of 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. 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 aim of the study is to discover if a treatment works, or how long it works.

End of study visits and ratings are specially important if subjects are likely to go 'off-study' because of their worsening condition. Otherwise, the results will give a falsely optimistic view of their experience.

9. Statistical considerations

The sample size, analysis plan, study duration and tactics for dealing with multiple outcomes, missing data, and attrition should be described briefly in this section. 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 needed to detect the minimum clinically important difference on the measure of effect for the primary endpoint with a specified test, level of confidence or significance, and power. The key decision is how small an effect warrants declaring the results '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, endpoints, attrition and missing data; all of which increase the risk of spurious results. The analysis plan should specify methods for dealing with these problems.

10. Feasibility

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

11. Significance

Explain what makes the study important and why it will be worthy of attention. What difference will doing this study make; in other words, what are the implications (likely consequences) of its findings (positive or negative)?

12. Funding

List potential sources of funding and their timing (application deadlines, decision dates, grant durations). List the arguments most likely to persuade potential funders. List strategies for improving the likelihood that funding applications will be successful.

13. Risks

What are the main threats to starting and completing the study? What are possible adverse consequences of doing the study? What can be done to mitigate these hazards?