Specifying objectives and outcomes for clinical trials

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THOROUGH DEFINITIONS and descriptions of the objectives and outcomes in clinical trials lead to results that are more readily interpretable and more easily generalisable. Indeed, the failure to prospectively define both objectives and outcomes in sufficient detail, and to describe how these are to be measured, has been a major criticism of some randomised trials.[1] Items 5 and 6 of the CONSORT statement checklist relate to objectives and outcomes in randomised trials.[2]

1: CONSORT checklist of items to include when reporting a trial

Selection and topic	Item no.	Description
Objectives	5	Specific objectives and hypotheses
Outcomes	6	Clearly defined primary and secondary outcome measures and, when applicable, any methods used to enhance the quality of measurements (eg, multiple observations, training of assessors)

Objectives

These should be *clearly* defined, and stated in a manner that will allow the objectives to be investigated by a quantitative assessment of appropriate outcomes. For example, an objective stating ". . . whether allowing free access to heroin will decrease the crime rate . . ." is too vague without a detailed definition of what constitutes a crime and how and when these are to be measured. Loosely stated objectives may appear in studies with a wide range of scientific rigour, and are likely to give rise to scepticism about the trial results, owing to concerns that the definitions may have been created *post hoc*, with foreknowledge of the study data. Concerns might also arise about studies whose objectives require myriad tests or assessments (eg, psychological, clinical and psychiatric), potentially confusing the reader as to which, if any, evaluated the primary hypothesis. The supporting evidence, outlined in the background and rationale of the study, should be linked logically to the study objectives.[3] The outcomes of studies are more convincing when they apply to a single or small number of clearly defined objectives.

The objectives should include:

- a precise statement of the degree of benefit expected from the intervention, as well as the duration of the benefit;
- clear statements of the time frame of the study (especially in relation to how quickly benefits might commence); and
- a definition of the patients for whom the benefit is sought.[4]

Objectives can be classified as either *primary* or *secondary*. Primary objectives provide the focus of the study. Collection and measurement of outcomes affecting the primary objective is critical and, if resources are scarce, these take priority over other aspects of the study. An exception to this is that the collection of safety information is always considered of high priority, regardless of whether safety is the focus of the study. It is crucial to minimise missing data related to the primary objective. Secondary objectives allow for investigating subsidiary questions that, while scientifically important, do not have the same priority of clinical interest in the patient group being studied.

In most randomised trials, efficacy of the intervention or its equivalence with standard care is the primary objective, whereas safety (eg, toxicity, side effects) is usually a secondary objective.

Outcomes

As with the objectives, the outcomes of the trial require precise description and definition. Standard measurement criteria are essential in order for the results to be accepted by the clinical community. For example, in cancer studies, measuring response by tumour area is a widely accepted practice, whereas measuring response by tumour volumes may be questioned by those not routinely using this criterion. The outcomes chosen should be clinically relevant and, where possible, measured in an objective fashion. If objectivity in measurement of outcomes is not possible, some control, on a subjective assessment, is desirable. For example, blinding assessors to treatment allocation provides a powerful tool for reducing measurement bias.[5] The frequency of outcome measurement should be clearly stated, as should strategies to be undertaken if the pooled outcome rate is lower than anticipated (eg, adjustment of study sample size). As with objectives, outcomes can be classified as primary or secondary and the same comments relating to primary objectives also apply to the measurement of primary outcomes.

If multiple outcomes (eg, liver function test results, or scores on a battery of psychological scales) are measured, precise statements on which aspect of these will be used to investigate the objectives need to be made *a priori*. The analysis of multiple outcomes requires specialised statistical

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methods and these should defined in detail in the study protocol and report. Where it is essential to employ multiple outcomes, a priority list detailing which of the outcomes represents the benefit sought should be determined in advance. Thus, for example, if a series of haematological parameters is being measured, then a single parameter (eg, changes in the platelet count) should be defined as the primary outcome.

If an outcome is measured repeatedly (eg, muscle strength), the issue of how these repeated measurements will be used to meet the objectives needs to be clearly stated. Thus, an objective considering "the frequency of heroin use in the 28 days before a six-month assessment (ie, during month 5)" will require different outcomes measurement to an objective considering "the average frequency of heroin use over a six-month period". The latter objective would require specification of how often the frequency of heroin use was to be estimated or recorded over the six months. Missing measurements may also become an issue (such as measurement of heroin use in a self-reporting study) and requires careful thought in the design stage. It may be desirable to specify a secondary, "fallback" objective in case data for the primary outcome prove difficult to collect over the study period (a well conducted pilot study would avoid this risk).

Surrogate outcomes

In many instances the use of surrogate, or intermediate, outcomes allows for shorter study durations (because surrogate events accumulate faster), with results on the surrogate outcome being translated to an outcome of major clinical interest. A surrogate outcome is one that is intended to capture the treatment effect on an important clinical endpoint, but does not directly measure the main clinical benefit of the intervention. For example, in cancer studies, tumour response, disease-free survival and time to disease progression have been used as surrogates for survival. The conditions under which an outcome is a "good" surrogate are still the subject of research.[6] Nevertheless, many surrogate outcomes (eg, elevated tumour marker levels as indicators of tumour activity, such as prostate specific antigen in prostate cancer) provide strong associations with tumour growth as an important question of interest. Statistical methods exist to examine the degree to which a surrogate is associated with a main outcome,[7] although these are still being refined. A statement indicating how and how much of any benefit observed in the surrogate will translate to the main clinical outcome should be provided.

In clinical studies, where it is not feasible to have adequate statistical power for a clinical endpoint, a valid surrogate may be used as the primary objective, with the main clinical endpoint becoming a secondary objective.

2: Checklist for objectives and outcomes in clinical trials

Objectives

- Are the intervention and control (eg, usual care) described in detail?
- Has the the target patient population been specified?
- Has the degree of benefit from the intervention on a particular outcome, and the time frame, been specified?
- Has the primary outcome, including how and when it is to be measured, been specified?
- Have any secondary outcomes been pre-specified in similar detail?

Outcomes

- Are the outcomes clinically relevant, objective (wherever feasible) and unambiguous?
- Can the outcomes be measured for all patients and, where possible, assessed with researchers blinded to the allocated treatment?
- Is the study explicit in the frequency and duration of outcome measurement?
- Has the study been specially planned from a statistical viewpoint when multiple outcomes are measured?
- If the outcome is a surrogate, will it adequately reflect a main outcome, and is there an indication of how much a benefit observed on the surrogate outcome will translate to a benefit on a main outcome?

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