Assessment of outcomes

Assessment of outcomes is vital to the interpretation and generalisability of study results.

Issues related to assessment include: the definition, the quality of measurements, the nature of any missing data, and blinding.

There are different types of outcome.

The primary and secondary outcomes should be specified a priori.

Assessment issues

Definition. The definition of an outcome is extremely important (Keech et al. 2007, p. 22). Care must be taken to make the definition precise, but not too specific or too general. For example, to classify an individual as having severe adverse toxic effects, such effects could be listed. The effects could be either self-reported, clinician-assessed or adjudicated by an independent panel of experts. For some outcomes, their severity may also be important (say, the grade of toxicity or intensity of pain), and accepted criteria should be used to determine an individual’s classification. When determining measurement of outcomes of this nature, the frequency of reporting and any delay in assessing outcomes are important issues in the scientific design of the study.

Quality of measurements. The quality of measurements can often be improved by taking multiple measurements. This can reduce the variability of a difficult measurement such as blood pressure (Prisant et al. 1996) and provide a more reliable and useful overall summary measure. Quality of outcome measurements can also be improved by providing training and giving clear instructions to all those involved in assessing the outcome. This is commonplace in multicentre trials, where consistency across sites is crucial.

Missing data. Missing data must be considered carefully. It is important to understand and record reasons why data are missing, as this may have an influence on how the data are eventually analysed, the interpretation of the results, and the conclusion reached on the value of the intervention. Quite commonly, in population-based studies of the elderly, people who drop out tend to be older and to be in poorer health than continuing participants (Chatfield et al. 2005). Ignoring them in such studies would lead to underestimates of individual cognitive decline.

Blinding. To avoid outcome bias in controlled trials, outcomes should be assessed by individuals who are blinded (that is, not aware of the treatment that the subject they are assessing has been allocated to) so that they cannot consciously or unconsciously influence the assessment to favour one of the groups being evaluated.

Key assessment issues *

<table>
<thead>
<tr>
<th>Outcome type</th>
<th>Issues</th>
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<tbody>
<tr>
<td>Traditional clinical: for example, survival, event rates, toxicity, cholesterol levels</td>
<td>Blinded assessment, uniform ascertainment, competing risks</td>
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<tr>
<td>Complementary: for example, health-related quality of life, patient utility, economic evaluations</td>
<td>Completeness of data, precise definition of endpoints, appropriate collection of resource use</td>
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<tr>
<td>Multiple</td>
<td>Consistency of results across the multiple outcomes, statistical issues</td>
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<tr>
<td>Molecular markers</td>
<td>Definition of positive signals or patterns, multiplicity and statistics</td>
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*Based on Gebski, 2004

Different types of outcome

There are many different types of outcome. Recently, more subjective or “softer” outcomes have been of interest. These are rated by patients or carers in combination with, or in place of, traditional outcomes based on clinical endpoints. Additionally, biomarkers and intermediate or surrogate outcomes (such as progression-free survival in oncology trials) are being more commonly employed in trials as a more practical endpoint for a disease which may take some time to mature. A concern with surrogate outcomes is the degree to which they are related to the true outcome of interest. In general, a very high degree of association is required before their use appears truly justified. Biomarkers as surrogates has now become extensive, especially in rare diseases.
Assessment of outcomes

such as in prostate cancer (prostate-specific antigen (PSA) (Denham et al. 2008)) and ovarian cancer (Ca-125 levels). These have clinical attraction but their relationship to the clinical endpoint is still being evaluated.

Specifying the primary and secondary outcomes

While the consistency of results across the multiple outcomes is important and should be carefully examined, it is also important to specify a priori which outcome, where possible, is the most important outcome; that is, it answers the most important scientific question being asked. This helps readers in knowing how much emphasis to place on significant results. In many studies outcomes are composites (for instance in a cardiovascular study, a composite outcome may be cardiovascular death, or stroke, or revascularisation, or any combination of these), and in such instances, care is required to properly interpret the results of the comparisons when different combinations of events make up the outcome. These have led to difficulty in the clinical interpretation of such studies. Multiple outcomes bring with them concerns about the statistical issue of multiplicity — whereby testing of many outcomes and associations will produce some significant results just by chance alone. (There is a 5% chance of getting a significant result if $P<0.05$ is considered to be significant on a single test. If no adjustments (such as Bonferroni correction) are made, there is a 40% chance of finding at least one significant result on 10 independent tests.) This principle is a very important one. It is sometimes hard to implement, and one exception to this principle may be studies examining gene and proteomic expression data, although the issue of multiplicity is still troublesome.

References


Contact the Outreach team (trials@ctc.usyd.edu.au) or go to the CTC website (www.ctc.usyd.edu.au/our-research/ctc-outreach.aspx) for further advice.