

METHODS FOR DETERMINING THE TARGET DIFFERENCE FOR A RANDOMISED CONTROLLED TRIAL

Methods for determining an important difference

- *Anchor:* Under such an approach the outcome of interest is “anchored” by using either a patient’s or health professional’s judgement to define an important difference. This may be achieved by comparing before and after treatment and then linking this change to participants who had an improvement/deterioration. Alternatively a contrast between patients can be made to determine a meaningful difference.
- *Distribution:* This covers approaches which determine a value based upon distributional variation. A common approach is to use a value that is larger than the inherent imprecision in the measurement and therefore likely to represent a minimal level for a meaningful difference.
- *Health economic:* This covers approaches which make use of the principles of economic evaluation and typically involves defining a threshold value for the cost of a unit of health effect that a decision-maker is willing to pay and using data on the differences in costs, effects and harms to make an estimate of relative efficiency. This can be based upon a net benefit or value of information approach which seeks to take into account all relevant aspects of the decision and can be viewed as implicitly determining a target difference.
- *Standardised effect size:* Under such an approach, the magnitude of the effect upon a standardised scale is used to define the value of the difference. For a continuous outcome, the standardised difference (most commonly expressed as Cohen’s “effect size”) can be used. Cohen’s cutoffs of 0.2, 0.5 and 0.8 for small, medium and large effects are often used. Binary or time-to-event outcome effect metrics (e.g. a risk or hazard ratio) can be utilised in a similar manner though no widely recognised cutoffs exist. Cohen’s cutoffs approximate to odds ratios of 1.44, 2.48 and 4.27 respectively. Corresponding risk ratio values vary accordingly to the control group event rate.

Methods for determining a realistic difference

- *Pilot study:* A pilot (or preliminary) study may be carried out where there is little evidence, or even experience, to guide expectations and determine an appropriate target difference for the trial. The planned definite study can be carried out in miniature in order to inform the design of the future study. In a similar manner a Phase II study could be used to inform a Phase III study.

Methods for determining an important and/or a realistic difference

- *Opinion-seeking:* This includes formal approaches for determining the target difference on the basis of eliciting (often a health professional’s although it can be patient’s or other’s) opinion. Possible approaches include forming a panel of experts, surveying the membership of a professional or patient body or interviewing individuals. This elicitation process can be explicitly framed within a trial context.
- *Review of evidence base:* The target difference can be derived using current evidence on the research question. Ideally, this would be based upon a systematic review of RCTs, and possibly meta-analysis, of the outcome of interest which directly addresses the research question at hand. In the absence of randomised evidence, evidence from observational studies could be used in a similar manner. An alternative approach is to undertake a review of studies in which an important difference was determined.