

Clinical trial designs and sample size

Phase I, II, III clinical trials

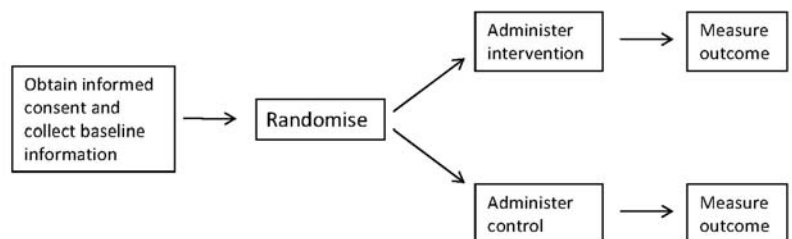
The process for generating evidence on the safety and effectiveness of an intervention generally commences with small trials that have an emphasis on preliminary information and may progress to larger confirmatory trials. Clinical trials may be categorised by phase according to where they fit in this research continuum. The initial trials, phase I trials, are used to characterise the properties of the intervention in an effort to optimise methods of delivery. For example, in the pharmacological setting, a phase I trial may be used to obtain information on the pharmacokinetic properties of a compound and identify a safe dosage range for subsequent therapeutic evaluation. Phase II studies are used to assess the feasibility and therapeutic potential of the given intervention. These studies commonly have no comparator intervention and are again modest in size. Given positive results in phase II testing, phase III studies may be undertaken to generate definitive conclusions about the merits of an intervention. These studies will typically employ a randomised-controlled design and are often much larger.

Common designs for phase III clinical trials

A phase III trial usually has two treatment arms. One arm is the control (placebo, standard care, etc.) and the other is the intervention. A randomised-controlled design is one in which allocation of a volunteer to either the control or intervention arm is determined by a chance mechanism. Randomisation ensures there are no systematic differences between the characteristics of volunteers in the two arms and helps ensure that the estimate of the treatment effect is unbiased. Concealing treatment allocation from all participants in trial activities (volunteers, clinicians, and other members of the study team) is another important design feature used to constrain the potential for bias due to preconceptions.

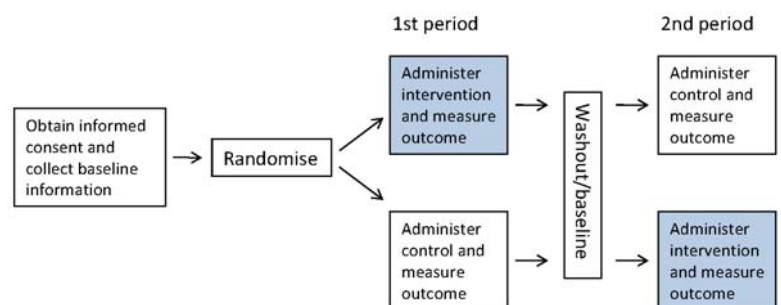
Parallel two-arm designs

Phase III trials are often undertaken as parallel two-arm design as shown:



Crossover designs

A crossover design may be useful in situations involving chronic stable conditions and where the intervention and control have fully reversible effects. In a crossover design, patients receive the intervention and then the control (or vice-versa), an order that is determined randomly. A washout period between treatments may be included in the design. These studies can be more efficient than parallel-group designs and consequently require fewer volunteers.



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Sample size

The number of volunteers required for a phase III study will depend on the expected size of the treatment effect (for example, a 10 mmHg difference in systolic blood pressure reduction), the degree of variability in the measure of effect (for example, variation in systolic blood pressure reduction scores across volunteers), and the extent to which the study team wishes to constrain the possibility of reaching a false-positive or a false-negative conclusion. The diagram shows the types of errors that can be made when drawing a conclusion from a typical two-arm randomised-controlled trial.

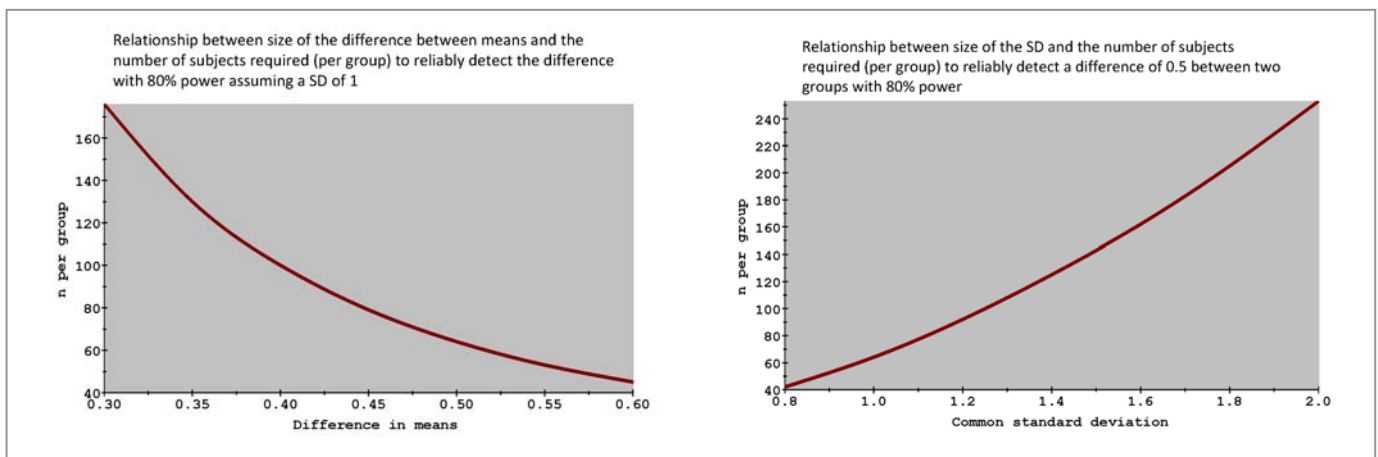
Type I error, type II error and power

		Reality	
		Treatment NOT Effective	Treatment Effective
Conclusion from Trial	Treatment NOT Effective	✓ Correct decision	✗ Type II error probability = β
	Treatment Effective	✗ Type I error probability = α	✓ Correct decision Probability = $1 - \beta$ $1 - \beta$ = power

Phase III trials are typically designed to constrain the probability of a type I error (known as alpha) to 5% and the probability of a type II error (known as beta) to 20%. The power of a study (to correctly identify a true effect exists) is equal to 1 minus beta.

More information (such as a larger study) is required to both improve the ability of a study to detect treatment effects (that may be modest in size in relation to the variability in the measure used to quantify the effect), and to minimise the risk of drawing an erroneous conclusion. These graphs (below) illustrate the influence that the size of the effect and the degree of variability in the measure of effect (quantified in the figure by a statistic known as the standard deviation (SD)) has on the sample size requirements for a hypothetical randomised-controlled trial.

Formulae based on statistical theory (and software that implements these formulae) are available to calculate the size required for a clinical trial, given various assumptions specified by the investigator relating to the nature of the efficacy measure (for example, binary, categorical, or continuous measure), the anticipated variability in the measure of effect, the size of the effect, and the choice of alpha and beta values.



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