Clinical Trial Design

2.2 The Importance of Clinical Trial Design

The overall objective in designing a clinical trial is to be able to provide the best possible and most reliable estimate of the effect and/or safety of a certain test article. Now, this estimate will never be conclusive, since it only observes a subsample of the entire participant population. There is always the possibility that the sample in question does not, in fact, fully represent the underlying population.

2.2 The Importance of Clinical Trial Design (2)

With this come two potential mistakes or errors:

(I) we concluded there was a difference between two treatment groups when there was, in fact, no difference (false positive result), or (II) we concluded there was no difference between two treatment groups when there was, in fact, a difference (false negative result). The objective is to identify the optimum trial design for the purpose of reducing the probability of false results; this is dependent on many factors, such as trial objectives, therapeutic area, treatment comparison and phase of clinical testing.

2.2 The Importance of Clinical Trial Design (3)

Biostatistics is an important science of clinical trials since it provides an estimate of probability for making any of those two false conclusions. For example: when we flip a fair coin 100 times, we expect 50 heads and 50 tails – but we can also get different numbers such as 60 and 40. In clinical trials the same variation arises because the random selection of participants typically involves many difficult or easy participants to one treatment over the other. Treatment A, which has a true treatment success rate of say 50%, could show 30 successes in 100 participants, while treatment B, which has a true rate of say 40%, could show 50 successes in 100 participants. Based on our total combined sample of 200, we could come to the wrong conclusion that treatment B is better than treatment A (a false result).

2.2 The Importance of Clinical Trial Design (4)

The basic problem is that the important characteristics of the random sample may or may not match the reality of the world, namely the entire participant population. And we rarely know how representative a subsample is of the real world. The point of clinical trial design and interpretation is to control the risk of making an error to discover the truth. We must decide what level of risk we can afford and rationally justify. Note that a false negative trial result will in practice end a particular development programme. This is costly not only to the trial sponsor, but also to society, which loses out on finding a potentially useful treatment.

2.2 The Importance of Clinical Trial Design (5)

Four different interpretations can be made from a clinical trial: either the two errors or correct interpretations that reflect the real world, i.e., the treatment is either effective or ineffective, where a false positive result is termed type I error, and a false negative result is termed type II error. The level of risk that we are prepared to take in reaching a wrong conclusion can also be measured by the cost of the trial. If we can afford a very large sample size – say, 10,000 rather than 10 participants – the risk of making type I/II errors will be reduced to a very small fraction. However, the cost of conducting the trial will increase by a factor of 1,000. From a research ethics point of view, we may also unnecessarily put many trial participants at risk by increasing the sample size without making a proper risk assessment.

2.2 The Importance of Clinical Trial Design (6)

The four types of interpretations that can be made from a clinical trial

		Trial interpretation: Effective	Trial interpretation: Ineffective
Real life: Effective		Success	False "negative" type II error
Real life: Ineffective		False "positive" type I error	Success

So, the main objective of a clinical trial design is to give the decision makers a probability measure for taking certain risks, weighed against the financial cost that must be invested to decrease the risk. The EC must have this information to be able to approve or reject a clinical trial protocol.

Clinical Equipoise

Equipoise can be defined as “balance” or “equability of distribution." In the context of clinical trials, “clinical equipoise” relates to the state of uncertainty regarding whether one of the alternative interventions, of, for instance, two study treatment arms, will give a more favourable outcome than the other. Under the principle of equipoise, a participant should be enrolled in a randomised controlled trial only if there is substantial uncertainty about which intervention will likely benefit the participant more than the other intervention(s). Clinical equipoise is a part of the EC review process, because it is critical to the research design – for instance, by setting up the research hypothesis and statistical testing and, perhaps, the number of participants to be recruited into one treatment group. It can also be the rationale behind interim data analysis during a trial, to identify findings that might change the clinical equipoise picture.

Superiority, Non-inferiority, and Equivalence Clinical Trials

The E9 ICH Guideline – "Statistical Principles for Clinical Trials" – that brings up the basic principles of designing and analysing clinical trials is highly recommended to be studied by any person involved in clinical trials (http://www.ich.org/LOB/media/MEDIA485.pdf). It is in fact surprisingly easy to understand.

This guidance contains a section addressing the type of comparisons made in certain clinical trials. The most common type of comparison trial is the so-called superiority trial, whereby efficacy is most convincingly established by demonstrating superiority to a placebo in a placebo-controlled trial or by showing superiority to an active control treatment.

Superiority, Non-inferiority, and Equivalence Clinical Trials (2)

However, sometimes an investigational product is compared to a reference treatment without the objective of showing superiority. Some active control trials are designed to show that the efficacy of an investigational product is no worse than that of the active comparative treatment, i.e., non-inferiority trials.

Other trials – equivalence trials – have the primary objective of showing that the response to two or more treatments differs by an amount that is clinically unimportant. This is usually demonstrated by showing that the true treatment difference is likely to lie between a lower and upper equivalence margin of clinically acceptable differences.

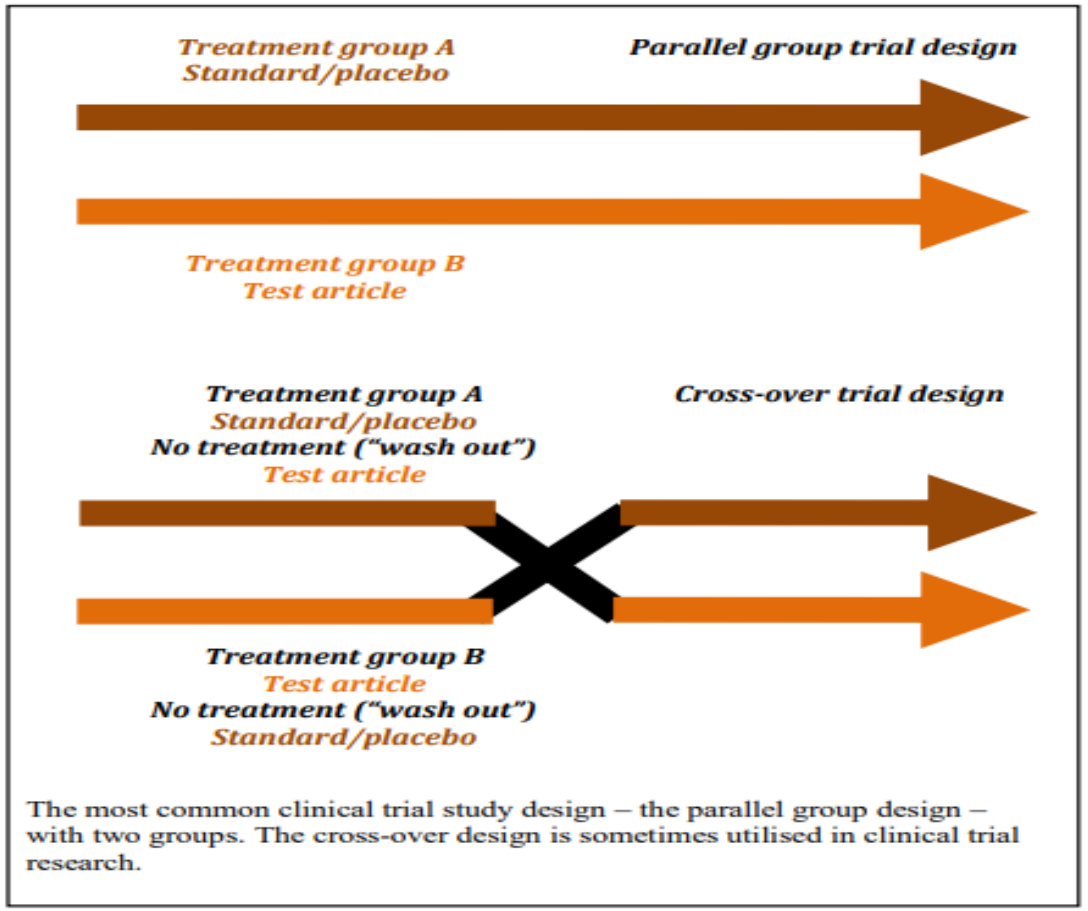
The choice of the type of comparison will influence some technical aspects of the study design, sample size and statistical analysis, but this will not be further elaborated in this Guide, where superiority trials are generally assumed to be the design of choice.

Types of Clinical Trial Designs

Most clinical trials use a fixed design that remains virtually unchanged during the duration of the trial. In those cases, the design is defined prior to trial initiation, which makes life easier for the EC. But some trials might not have enough information to correctly estimate the sample size beforehand. Here, the protocol might spell out that the sample size will be reassessed and revised at a certain point in time – it usually happens after a specific number of participants have completed a certain number of study visits. Increasing the number of visits or duration of the follow-up is also quite common with protocol amendments. Such changes will not usually affect the sample size and trial design in general, but an EC review is needed for any protocol amendments that may influence the risk of harm to participants.

A clinical trial design has many features and some of them are covered in other sections of this Section, i.e., controls, outcomes, randomisation, blinding, sample size and trial phases. Here, we address a few general, common trial design characteristics based on the number of groups and treatment alternatives. The most common type uses two parallel groups – parallel group design.

Types of Clinical Trial Designs (2)



The most common clinical trial study design – the parallel group design – with two groups. The cross-over design is sometimes utilised in clinical trial research.

Types of Clinical Trial Designs (3)

In most cases, trial participants are randomised to one of the two treatment groups, with randomisation commonly giving each participant the same possibility or chance to be allocated to either treatment section. One group – say group B – is given the test article, and the other group frequently given placebo (dummy) treatment, or the current best available treatment on the market (standard treatment). It is also possible to give both groups the standard treatment with the addition – as an add-on treatment or as a combination therapy – of the test article for one of the two treatment groups.

Types of Clinical Trial Designs (4)

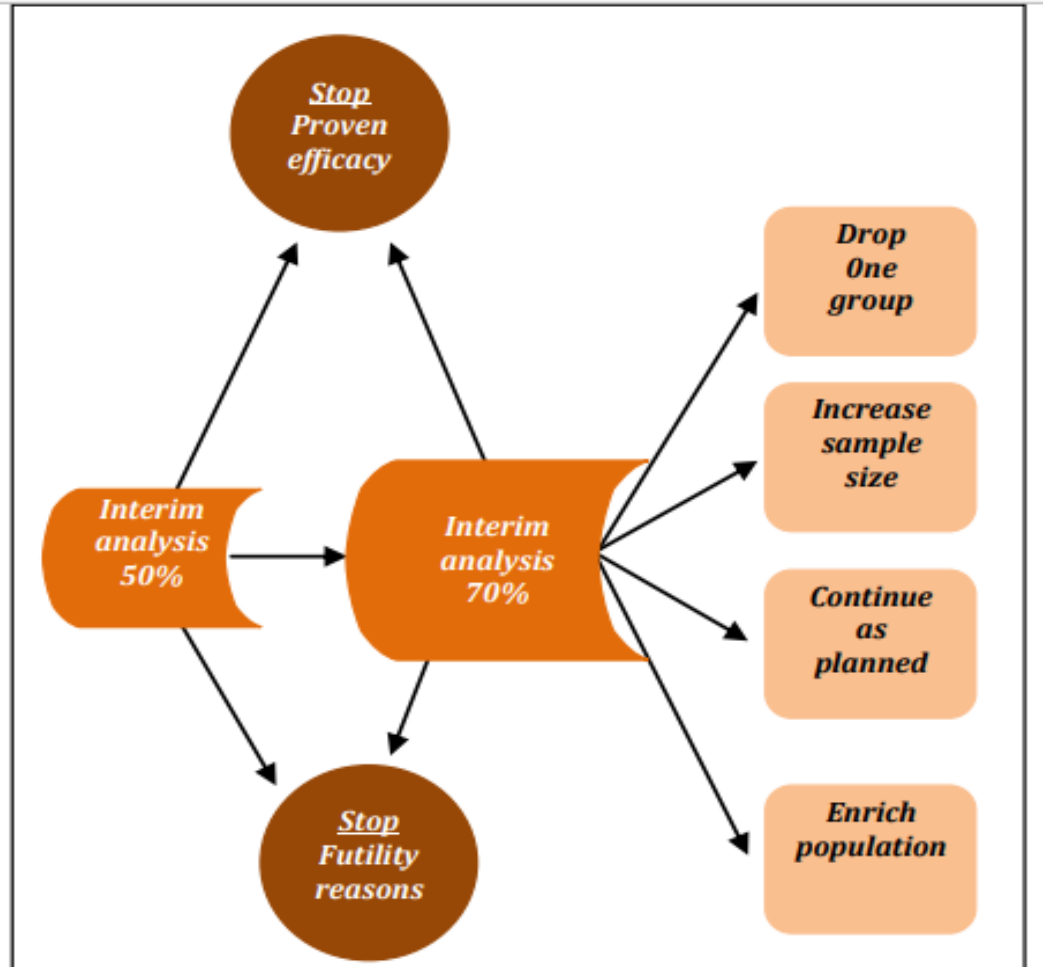
Another type of trial design is the cross-over trial design. Here, the trial participants receive both treatments in sequence. The cross-over design represents a special situation where there is not a separate comparison group. In effect, each participant serves as his/her own control. Some participants will receive the standard therapy or the placebo first, followed by the new therapy (AB). Others will receive the new therapy first, followed by the standard therapy or the placebo (BA). A cross-over design has the advantage of eliminating individual participant differences from the overall treatment effect. On the other hand, it is important in a cross-over trial that the underlying condition – for instance, a disease – does not change over time, and that the effects of one treatment disappear before the next is applied. With this, it follows that cross-over design is utilised much less commonly than parallel group design. The crossover design is also more sensitive to drop out during the trial, since participants act as a control as well as active treatment participants.

Types of Clinical Trial Designs (5)

An open-label trial – though less common – is when both the investigators and participants know which treatment is being administered, with trial participants still commonly randomised to one of two treatment groups. Using historical controls is nowadays seen as a sub-standard research design, since standard medical treatments change over time and randomisation to treatment cannot apply. Sometimes a trial has more than two concurrent treatment groups, for instance when different doses are to be compared.

Adaptive Clinical Trial Design

A few, but an increasing number of trials use the so-called adaptive clinical trial design – empowering sponsors to respond to data collected during the trial. Examples of adaptive trial designs include dropping a treatment group, modifying the sample size, balancing treatment assignments using adaptive randomisation, or simply stopping a trial early due to success or failure (see illustration).



Adaptive trial design – example of decision pathways. The term "futility" refers to the inability of a clinical trial to achieve its objectives. In particular, stopping a clinical trial when the interim results suggest that it is unlikely to achieve statistical significance can save resources that could be used on more promising research. An interim statistical analysis is a temporary or provisional arrangement for decision making only and will not allow any details of the results to be passed on to the investigator or participants.

Adaptive Clinical Trial Design (2)

In a standard trial, safety and efficacy data are collected and reviewed by a data safety and monitoring committee during scheduled interim analyses. However, aside from stopping a trial for safety reasons, very little can be done in response to these data. Often, a whole new trial must be designed to further investigate key trial findings.

A few, but an increasing number of trials use the so-called adaptive clinical trial design – empowering sponsors to respond to data collected during the trial. Examples of adaptive trial designs include dropping a treatment group, modifying the sample size, balancing treatment assignments using adaptive randomisation, or simply stopping a trial early due to success or failure (see illustration). In a standard trial, safety and efficacy data are collected and reviewed by a data safety and monitoring committee during scheduled interim analyses. However, aside from stopping a trial for safety reasons, very little can be done in response to these data. Often, a whole new trial must be designed to further investigate key trial findings.

Adaptive Clinical Trial Design (3)

Another example of adaptive design is response adaptive. In this setting, participants are randomised to treatment groups based on response to treatment of previous participants. Real-time safety and efficacy data can be incorporated into the randomisation strategy to influence subsequent adaptive randomisation decisions on a participant-by-participant basis. An example of response-adaptive randomisation is play-the-winner, which assigns participants to treatment groups that have resulted in fewer adverse events or better efficacy.

As these examples demonstrate, the adaptive design concept can be utilised in several different ways to increase trial flexibility. In a well-designed adaptive trial, that flexibility can result in lower drug development costs, reduced time to market and improved participant safety. Cost reduction is achieved by identifying successful trials sooner, dropping unnecessary treatment groups or determining effective dose regimens faster. Participant safety is improved because adaptive trials tend to reduce exposure to unsuccessful treatment groups and increase access to effective treatment groups.

Adaptive Clinical Trial Design (4)

Adaptive trial design requires modern data collection technologies to provide the research team with real-time information and enables them to plan and quickly implement seamless changes in response to that information. Key enabling technologies for adaptive trial design are, for instance, real-time electronic data capture over the Internet to a central database.

The general impression is that utilising adaptive clinical trial design will become more and more popular. The ECs will play a crucial role in this process, since they will be required to respond within a very short time to design changes so trials can be adjusted in a real-time manner. This calls for ECs to also become adaptable to change.