Phase III trials: typical trial designs

A phase III trial is typically designed to answer a specific clinical question, based on information or data from previous phase I or phase II trials, results of other studies and relevant available background information.

The main purpose of a phase III clinical trial is to bring the results from a clinical trial into general practice, to evaluate the specific therapeutic benefit of the intervention treatment and subsequently change clinical practice.

A phase III trial usually has two treatment arms. One arm is the placebo, control, or standard-care arm and the other arm is the intervention. Allocation to treatment arms is randomised.

Typical 2-arm simple parallel design

![Diagram of 2-arm simple parallel design]

**Advantages**
- The parallel design is usually the simplest and most frequently employed design
- If conducted correctly, it minimises bias through randomisation, prospective design, and, where possible, double blinding.

**Limitations**
- Patients receive only one treatment (this may or may not be a desirable feature.)
- For chronic or severe diseases, investigators need to be aware of potential therapy changes for the treatment of the disease and potential trial discontinuers (particularly for long-term follow-up studies)

2x2 factorial design

The general principle of this design is to evaluate two different (and apparently independent) interventions compared to a control in a single trial. It is a special case of a 4-arm parallel design.

As with a conventional parallel trial, each patient is randomised to one treatment arm only (out of all possible treatment arms available).

**Example**

<table>
<thead>
<tr>
<th></th>
<th>No vitamin A</th>
<th>Vitamin A</th>
</tr>
</thead>
<tbody>
<tr>
<td>No zinc</td>
<td>Arm 1</td>
<td>Arm 2</td>
</tr>
<tr>
<td>Zinc</td>
<td>Arm 3</td>
<td>Arm 4</td>
</tr>
</tbody>
</table>

Assume vitamin A only (Arm 2) versus neither (Arm 1) produces a similar treatment difference to Vitamin A and zinc (Arm 4) versus zinc only (Arm 3)

The 2 x 2 factorial design principle can be extended to ‘higher order’ factorial designs, such as a 2 x 4 factorial (two factors of interest, one factor with 2 levels, one factor with 4 levels), a 2 x 2 x 2 factorial (three factors of interest, each factor having two levels), etc.

**Advantages**
- Test two independent hypotheses (one for each of the interventions) without increasing sample size
- Gain experience of treatment combinations

**Limitations**
- Possible practical problems
- Problems of interpretation if any signs of interaction between the two interventions exists (that is, cannot simply describe the main treatment effects for Treatment X and Treatment Y)
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Cross-over design

In a cross-over design patients are randomised into one of two groups with a washout period between treatments

- **Group I**: treatment A followed by treatment B
- **Group II**: treatment B followed by treatment A

Advantages

- Reduce variability of the outcome measurement as the same subject is used twice, as an experiment and control
- Efficiency of design = 2.4 x participants required if a two-arm parallel design was used
- Can be employed for treatment of chronic diseases

Limitations

- Assumption of no carryover effect
- Assumption of stability of disease process, not suitable for acute diseases
- Limits response variable: cannot use ‘cure’ or clinical event
- Possible period effect if condition changes over time

Cluster randomised clinical trials

In some instances the application of a randomised clinical trial in areas away from the traditional use in clinical medicine may provide difficult. For example, evaluation of screening programs (breast cancer, cervical cancer, etc) or evaluation of health promotion strategies (e.g. use of sunscreen to prevent melanoma). Instead whole clusters (or groups) of patients must be allocated *en bloc* to a given treatment.

A cluster randomised trial can still be run as:

- Parallel design (cluster is randomised to receive one of two or more treatments and then followed over time or measured for outcome)
  - Simple parallel
  - 2 x 2 factorial
- Cross-over design (cluster receives all treatments in randomised order). This is less likely to happen with cluster trials, but possible.

Equivalence trials vs efficacy (comparative) trials

The majority of clinical studies are designed to test whether one or more experimental therapies is *better* than current standards. However, equivalence trials differ from efficacy or comparative studies in that they are designed to test whether one or more experimental therapies is at least as effective as standard therapy. Equivalence studies thus address the issue of whether one can replace an effective standard treatment with a new treatment which has an equivalent effect but may be easier or cheaper to administer.

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.