Treatment allocation and sample size

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Treatment allocation

- In clinical practice, treatment choice is based on what the clinician thinks might benefit the patient.
- In clinical trials, treatment choice is based on active control of treatment alternatives, and allocation processes.
- Aims to evaluate treatment effects while avoiding biases and confounders.
Main considerations

- Produce a balanced comparison
  - Reduces bias
- Quantify errors attributable to chance
  - Overall, this improves objectivity, and avoids a type of selection bias: “confounding by indication” (Miettinen, 1983)
- Important, because baseline characteristics predict treatment response
- Evens out both known and unknown confounders
• Haphazard assignments (eg date of birth, date of enrollment) are not random
  – Cannot be relied upon to reduce bias
  – Solution: Randomisation

• Implementation of randomised treatment allocation for clinical trials appears as though it should be straightforward (Piantadosi, 2005)
  – …but it usually isn’t
Types of randomisation

- Simple randomisation e.g., coin toss is random in theory (law of large numbers) but not in practice as clinical trials usually have small numbers.

Would need ~400 trials to be random in this example.
Randomisation methods: constrained randomisation

- **Blocking**
  - each block contains a pre-specified number and proportion of treatment assignments

### TABLE 13.1 All Possible Permutations of Two Treatments in Blocks of Size 4

<table>
<thead>
<tr>
<th>Within-block Assignment Number</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>A</td>
<td>A</td>
<td>A</td>
<td>B</td>
<td>B</td>
<td>B</td>
</tr>
<tr>
<td>2</td>
<td>A</td>
<td>B</td>
<td>B</td>
<td>B</td>
<td>A</td>
<td>A</td>
</tr>
<tr>
<td>3</td>
<td>B</td>
<td>A</td>
<td>B</td>
<td>A</td>
<td>B</td>
<td>A</td>
</tr>
<tr>
<td>4</td>
<td>B</td>
<td>B</td>
<td>A</td>
<td>A</td>
<td>A</td>
<td>B</td>
</tr>
</tbody>
</table>

Regardless of permutation, 2A’s & 2B’s, can be combined in 6 different ways.
• You can stratify blocking for a prognostic factor / confounder

Blocking can improve the power of trials by reducing unwanted variation (Palta, 1985)

BUT

If block size is too small, or too many strata, then randomisation is predictable

Piantadosi, 2005 “Clinical trials: a methodologic perspective”
Randomisation methods: Adaptive allocation

- Probability of assignment to the treatments is determined by the current balance of the group

Only first person receives truly random allocation

Randomisation program written by someone with good database / programming skills

Piantadosi, 2005
Treatment blinding

• Outcome assessment is optimised if the person(s) observing experimental outcomes is objective
• Solution: Blinding
• Likely to have largest effect for subjective outcomes
• Ideally the following persons should be blinded to treatment allocation:
  – Patient (single-blind)
  – People assessing outcomes (double-blind)
• Often done by the use of placebos
• Not always possible to blind treatments eg physiotherapy vs surgery
• Adequately powered trials ensure that a difference is detected if it exists
• Underpowered trials can lead to false negative results (type 2 error = $\beta$)

Table 1. Overview of errors in clinical research

<table>
<thead>
<tr>
<th>Population</th>
<th>Difference does not exist</th>
<th>Difference exists</th>
</tr>
</thead>
<tbody>
<tr>
<td>Difference does not exist</td>
<td>False negative result Type II error (beta)</td>
<td>Power (1-$\beta$)</td>
</tr>
<tr>
<td>Difference exists</td>
<td>False positive result Type I error (alpha)</td>
<td>Power (1-$\beta$)</td>
</tr>
</tbody>
</table>

Noordzij, 2010
Items of information required for sample size calculations

- a proper hypothesis
- Magnitude of effect: Minimum clinically significant difference, effect size
- Variability: standard deviation, standard error
- Type 1 error (alpha), usually $\alpha=0.05$
- Power= $1-\beta$, where $\beta$= type 2 error. Usually 80% ($\beta=0.2$) or 90% ($\beta=0.1$)
- Use the literature to help you find reasonable estimates of trial parameters
Conceptualising sample size

Null hypothesis

Alternative hypothesis

Piantadosi, 2005

$T_{crit} = 1.96$

$\alpha = 0.05$

Calculations are approximations: if you really had the data no need for a trial

$\text{SS} \uparrow \text{as:}$
- difference between $H_0$ & $H_a$ $\downarrow$
- required power $(1-\beta) \uparrow$
- If 2 tailed test (usual)

Piantadosi, 2005
• Repeated measures? What’s the correlation between timepoints?
• Loss to follow up (often 20%)
• Allocation ratio (usually 1:1)
• Can calculate power from known n’s
• Different calculators are available to estimate SS for proportions (data from 0 to 1)
What to do now?

• Avoid the temptation to do a quick and dirty SS calculation
• Think about reality (dropouts etc)
• Get help from a statistician early
  – Come with relevant information
• If you can’t get access to a statistician, calculators on the internet