Randomisation

Randomisation is the method which attempts to allocate participants into the treatments under consideration.

Well conducted randomised study ensures that differences in effects observed are either true effects or occur through the play of chance.

Randomised comparisons provide unbiased estimates of the true underlying treatment effects and hence provide a high level of evidence as to the potential benefit of new therapies over standard treatment (controls).

When designing a study a randomised control trial (RCT), if well conducted, will assure practitioners that the highest level of evidence is provided comparing therapies. This has the advantage of influencing practice and health policy.

Sources of bias include

- Selection bias – since the treating clinician is unaware of the treatment being allocated, he/she cannot (unwittingly or on purpose) select patients to receive the active treatment which are in some way different from those receiving the control treatment.
- Confounding (accidental) bias. Even after randomization, when sample sizes are small it is possible there may be other prognostic factors related to the outcome which will end up being unbalanced and this may mask the effect of treatment. This can be addressed through stratified randomization

A non-randomised trial cannot be defended against claims of biased results.

Definition

Randomisation is the process of allocating study treatment(s) to subjects in order to minimize bias.

When to randomise?

The general sequence of events in a clinical trial is as follows:

Step 1: Clinician willing to be involved in the study
Step 2: Patient requires treatment for condition or disease
Step 3: Patient eligible for the trial
Step 4: Patient willing to accept randomisation
Step 5: Patient consent obtained
Step 6: Enrolment form completed
Step 7: Patient formally entered onto the trial
Step 8: Treatment assigned (via a randomisation scheme)
Step 9: Treatment started as soon as possible
Step 10: Study forms completed

Allocation concealment

It must not be possible for a clinician or investigator to identify the next treatment to be allocated in a trial. If the next treatment to be allocated is known, investigators may not offer the trial to some patients (or encourage patients to participate).

Allocation concealment should not be confused with blinding. Allocation concealment is always possible by safeguarding the assignment sequence before the treatment commences. Blinding is the process of keeping the treatment undisclosed after allocation has occurred and is not always possible.

Randomisation should be performed by an independent central person (not the investigator or the patient’s clinician or nurse). Centralised randomisation provides a strong guarantee of allocation concealment of treatments prior to randomisation and reduces the chance that a patient or clinician can guess the next treatment.
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Types of blinding

**Singlen-blind trial**
- patient unaware of treatment they receive
  example: different equipment used in surgery procedures

**Double-blind trial**
- patient and investigator unaware of treatment allocation
  example: numbered kits with treatments (e.g. tablets, syrup, etc.) which appear identical

**Stratification**
Some prognostic factors (such as age, stage at which cancer was diagnosed) may affect the outcome of interest and therefore introduce sources of bias. To increase the balance between treatments within the levels of key prognostic factors, randomisation can be stratified on these factors. For example, in a cancer trial, randomisation could be performed such that equal numbers of patients within each stage (e.g. III and IV) are allocated to both treatment arms.

Stratification improves confidence in positive trial results and should be considered if:
- the effect of treatment is potentially different in subgroups of patients (e.g. suspect that treatment is more effective in patients with diabetes than in those without)
- subgroups of patients are known to differ in the outcomes under consideration (e.g. risk of stroke is higher in older patients than younger patients).

**Randomisation methods**
- simple randomisation (e.g. tossing a coin)
- permuted blocks (with or without stratification), a system that ensures that after every 2, 4, 6… patients have been allocated a treatment there are equal numbers in each treatment group.
- adaptive allocations, such as minimisation, which determines treatment allocation based on the *stratum profile* of the current patient awaiting randomisation and the *current number of patients* in each stratum (and treatment) level.

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.