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Understanding controlled trials

Randomisation methods in controlled trials

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The main purpose of randomisation is to avoid bias by distributing the characteristics of patients that may influence outcome randomly between treatment groups so that any difference in outcome can be explained only by treatment. These characteristics might be demographic ones such as age or prognostic factors such as clinical history or disease severity. For example menopausal status may influence outcome of treatment for breast cancer.

The most elementary form of randomisation is, in the case of two treatments, equivalent to allocating treatment by tossing a coin. Lists for allocating patients by simple randomisation may be constructed with tables of random numbers or random functions on pocket calculators or statistical software. Treatments may then be allocated to patients in sequence using numbered opaque envelopes containing treatment allocations or remotely by phone.

While such simple randomisation will on average allocate equal numbers to each arm, even in quite large trials simple randomisation can result in groups of different sizes. In small trials there may be substantial differences in group sizes that will reduce the precision of estimates of the difference in treatment effect and hence efficiency of the study.

One method to prevent unequal treatment group sizes is block randomisation. This guarantees that at no time will the imbalance be large and at certain points the numbers of participants in each group will be equal. If, for example, we choose blocks of four, there are six sequences to which we can allocate treatments A and B: AABB, ABAB, ABBA, BAAB, BABA, and BBAA. One of the six arrangements is selected randomly and then four participants assigned accordingly. The process is then repeated as many times as is needed for the required sample size.

With simple randomisation or block randomisation substantial imbalance in prognostic characteristics can, nevertheless, arise by chance and can bias the analysis of outcome. One method to achieve balance between groups for a prognostic variable is stratified randomisation, in which separate randomisation lists are used for each prognostic subgroup. For example, in a study of alternative treatments for breast cancer it would be advantageous to stratify on menopausal status. Separate randomisation lists would be prepared

for each stratum using a block randomisation. It should be noted that using simple randomisation with each stratum would defeat the purpose of stratification as the resulting randomisation would be no different from simple randomisation. A standard practice in multicentre trials is to stratify randomisation by treatment centre.

Stratification may be extended to two or more factors, although the number of separate randomisation lists rapidly becomes very large. For example, if one was to stratify on three prognostic variables, with each having just two levels, eight separate randomisation lists would be required for each combination of factors. In practice therefore it is rarely feasible to go beyond two factors.

Stratified randomisation makes the process more elaborate and brings with it the risk of mistakes that the simpler methods might prevent. If there is uncertainty about which patient characteristics may influence the outcome of treatment it may be prudent to proceed without stratification.¹

An alternative method of obtaining treatment groups that are comparable in prognostic variables is minimisation. This achieves balance on a set of prognostic factors, although not for each combination. Even in small trials it will provide groups that are very similar on several prognostic factors. For all levels of each prognostic factor on which the investigator wishes to maintain balance, a running total is kept of how many patients have been assigned to each treatment. At the start of the trial treatment is randomly allocated to the first patient. Subsequent patients are assigned using a randomisation weighted towards the group to which assignment would minimise the imbalance. After each patient is entered the relevant totals for each factor are updated ready for the patient. Details with examples of the minimisation method are discussed by Pocock¹ and Altman.²

Whatever method of allocation is used, the process of allocation needs to be done in such a way that the randomisation cannot be deciphered, a topic discussed in a forthcoming note.

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