Randomisation: Magical Cure for Bias?

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Introduction

There is general consensus that randomised clinical trial (RCT) can provide the most valid conclusions about effects of different treatment as eligible patients are randomly allocated into two or more alternative treatments. Trials using non-randomised comparison groups like historical controls tend to yield more optimistic results than randomised trials.[1,2] It is believed that random allocation will remove the "selection bias", which is present when comparison groups are assembled in some other way.[1] Another reason for randomisation is that the computation of sampling errors is based on random sampling. Hence, if the selected samples behave like random samples, the observations can be compared with what we would expect if there were no difference in treatment effects (null hypothesis). However, since most tests of statistical significance are fairly robust, randomisation is used primarily for the control of selection bias.

Methods and Limits of Randomisation

Randomisation in clinical trials means that each patient has a known chance (in most instances, an equal chance) of being selected for each treatment but the treatment to be given cannot be predicted. Hence, the simplest method is to divide patients into two similar groups and at the last moment, allocates the entire group to their respective treatments by the toss of a coin. Van Helmont, a medicinal chemist in 1662, first proposed this method. He challenged the academics of the day to compare the outcomes of their treatment with his own. "Let us take out of the hospitals, out of the Camps, or from elsewhere, 200 or 500 poor People, that have Fevers, Pleurisies, etc. Let us divide them into half, let us cast lots that one half of them may fall to my share, and the other to yours. We shall see how many funerals both of us shall have."[3] This approach of randomising the entire group of patients suffers from the inability to assess random errors[3] and can be overcome by randomising individual patients.[4]

A common approach is to assign alternate patients into different treatments. In principle, this is a random and unbiased process. In practice, however, bias can arise because the treatment is known when a patient is considered for recruitment. This knowledge may unconsciously (or even consciously) influence the decision on recruiting the patient. A similar argument can be used for randomisation according to the date of birth, date of enrolment, day of the week etc. A simple solution is to blind the treatments, identifying them only as A and B. A further refinement is to blind the person conducting the recruitment from the outcome of the ongoing trial.

The time-honoured method of tossing a coin for the treatment choice as each patient presents is still acceptable. Using a random number generator (from tables or software) adds sophistication. The problem is that as the trial proceeds, the number in each arm may not be balanced.

In block randomisation, subjects are considered in blocks of say four at a time. It is useful to use multiples of the number of treatments and to use as small a block size as possible to allow for better control of the balance. Using block size of four for two treatment arms, there will be six possible blocks:

AABB BBAA ABAB BABA ABBA BAAB

Random numbers from 1 to 6 are selected and the blocks of patients will follow the selected combination. It is clear that a potential selection bias could occur if the recruiter knows in advance the selected combination. Hence, it is important to ensure that the recruiter and the person assigning the treatment are not in communication. Randomly altering the block size will also minimise the potential bias of predetermining the treatment choice of the last member of the block.

Randomisation removes bias in the treatment allocation process. However, it does not guarantee that the groups are identical in terms of important prognostic indicators. In fact, with small sample size, it is very likely that chance imbalance would occur. In many studies, important prognostic factors are known before the study. Separate block randomisation lists can be prepared for each stratum (stratified sampling). It is important to note that block randomisation should be used for each strata rather than simple random sampling. The use of simple random

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sampling in each stratum will lead to loss of treatment balance making the stratification ineffective.

Stratified sampling is impractical with multiple strata. Some combinations of categories may turn out to be very small. An alternative is a procedure known as minimisation. This is strictly not a random process but for small samples, it is acceptable and provides samples that are comparable for the various prognostic variables.[5] The basic principle is to give a higher probability for subjects to be recruited into the treatment arm, which has smaller number of subjects. For example, after randomly allocating a number of subjects, there are 3 more patients in treatment A than treatment B for a particular stratum, the next patient from this strata who is selected will be assigned to treatment B or be given a higher probability for its selection (say 0.75). This method has also been shown to be theoretically valid.[6]

Conclusion

Theoretically, randomisation is capable of controlling for known and unknown differences between comparison groups. Randomisation can only work its magic if there is unpredictability in the treatment assignment. Blinding the trialist who recruits the patients is crucial to prevent selection bias from creeping into a randomised trial.

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