

## Randomising patients in practice

### Why?

There are ethical and scientific reasons for randomising patients, but the most important aim is to avoid *selection bias*. If the researcher knows beforehand which therapy the next patient will receive, this may affect how they recruit. Systematic reviews have demonstrated selection bias to be a major cause of misleading results.

*Concealment* of the randomisation codes is therefore ESSENTIAL. Nobody involved in the recruitment of patients should help to prepare the randomisation lists.

*Third party randomisation* is the gold standard for concealment. A central office holds the allocation codes, usually on computer. Having recruited a patient, the researcher contacts the office. The office records patient details before telling the researcher the allocation.

*Concealed envelopes*, despite evidence of failure in some studies, are a cheaper and widely accepted alternative. Each allocation is written on paper and concealed in a serially numbered, opaque envelope. The researcher then opens the next envelope AFTER recruiting each patient. If resources allow, envelopes like those used for pay slips can be printed.

*Breaking the code* after allocation must be possible, especially in pharmaceutical trials. If a patient requires emergency treatment, knowledge of current therapy may be vital. You should consider at the outset how to allow access to records in an emergency without otherwise compromising concealment.

### How?

With any procedure the aim is to create a list of codes, so that the next patient receives a randomly allocated treatment. In a trial of two therapies, A and B, the list may look like AABBABAA. This is shorthand for patients 1,2,5,7 and 8 will receive therapy A, and patients 3,4 and 6 will receive therapy B.

Tossing a coin may seem like an adequate randomisation procedure. You could, for example, say “Heads and we give therapy A, Tails and it’s therapy B”. In practice, random number tables are preferable because you can document the allocation procedure (table, starting point, direction of reading). Documentation is good research practice as it allows independent verification of procedures. Computer generated random numbers may also be used.

Random No. Table
33 60 64 44 32 31 70
07 77 27 84 46 77 25
60 64 69 46 <u>68</u> 27 55
84 84 62 91 71 99 19
74 25 81 35 14 01 43

*Simple Randomisation* is like tossing a coin. The simplest case is a two-group study with the same number of patients in each group. You can have odd numbers for Group A and even numbers for Group B. Pick a start point on the table by closing your eyes and stabbing the page with a pencil. Then read down the table (or across, but decide beforehand) listing the order of odd and even numbers. For example, beginning at the point marked in the example table, the sequence 67126814 would produce the list BAABBBAB. The first, fourth, fifth, sixth and eighth patients would receive therapy B, and the second, third and seventh would receive therapy A.

For studies with three equal groups you may choose to use the numbers {1,2,3} for Group A, {4,5,6} for Group B, and {7,8,9} for Group C. Simply ignore any 0’s. The same number sequence as above, 67126814, would then produce the list BCAABCAB. It is important to decide which numbers designate which groups and the direction of reading (down or across) BEFORE selecting a starting point.

This technique works for any number of equal or different sized groups. For example, two groups in a 3:1 ratio could use {1,2,3,4,5,6} for Group A, {7,8} for Group B, and ignore 9’s and 0’s.

The disadvantage of simple randomisation is that it may give groups of different sizes. In the first example there were 3 group A patients and 5 in group B. For this reason simple randomisation is seldom ever used.

*Block randomisation* is sometimes called 'random permuted blocks'. A block of size four means that after every four recruits there will be the right numbers of patients in each group. To do this, first write down all possible orders (permutations) of four allocations and code them:

1=AABB    2=ABAB    3=ABBA    4=BAAB    5=BABA    6=BBAA

Then use simple randomisation to allocate the next block of 4 patients (ignore numbers 7,8,9,0 in the random number list).

The sequence 67126814 now produces BBAA AABB ABAB BBAA AABB BAAB.

In practice, a block size of four is too small since researchers may crack the code and risk selection bias. Mixing block sizes of between 6 and 12 is better. This precaution maintains concealment. Simple randomisation should determine which block size to use next.

*Stratified randomisation* ensures that important prognostic factors are balanced across groups. Typical examples of such factors are age group, severity of condition, and treatment centre. Stratification simply means having separate block randomisation schemes for each combination of characteristics ('stratum'). For example, in a study where you expect treatment effect to differ with age and sex you may have four strata: male over 65, male under 65, female over 65 and female under 65. If using envelopes, colour coding the separate schemes reduces the scope for errors. It is worth considering that for each factor which is stratified it can no longer be the outcome measure which is compared. So in the above example, age would not longer be comparable between the sex groups, or any other factor.

Stratification works with just one or two factors but becomes impractical with more. For example, if you wished to stratify by three levels of severity, two racial groups, sex and three age categories, you would need to organise 36 ( $3 \times 2 \times 2 \times 3$ ) separate lists. When it is essential to balance a number of prognostic factors, consider minimisation (see *BMJ* 1998;317:362-3) as an alternative.