Statistics Notes

Treatment allocation by minimisation

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In almost all controlled trials treatments are allocated by randomisation. Blocking and stratification can be used to ensure balance between groups in size and patient characteristics.[1] But stratified randomisation using several variables is not effective in small trials. The only widely acceptable alternative approach is minimisation,[2 3] a method of ensuring excellent balance between groups for several prognostic factors, even in small samples. With minimisation the treatment allocated to the next participant enrolled in the trial depends (wholly or partly) on the characteristics of those participants already enrolled. The aim is that each allocation should minimise the imbalance across multiple factors.

Table 1 shows some baseline characteristics in a controlled trial comparing two types of counselling in relation to dietary intake.[4] Minimisation was used for the four variables shown, and the two groups were clearly very similar in all of these variables. Such good balance for important prognostic variables helps the credibility of the comparisons. How is it achieved?

Minimisation is based on a different principle from randomisation. The first participant is allocated a treatment at random. For each subsequent participant we determine which treatment would lead to better balance between the groups in the variables of interest.

The dietary behaviour trial used minimisation based on the four variables in table 1. Suppose that after 40 patients had entered this trial the numbers in each subgroup in each treatment group were as shown in table 2. (Note that two or more categories need to be constructed for continuous variables.)

The next enrolled participant is a black woman aged 52, who is a non-smoker. If we were to allocate her to behavioural counselling, the imbalance would be increased in sex distribution (12+1 v 11 women), in age (7+1 v 5 aged >50), and in smoking (14+1 v 12 non-smoking) and decreased in ethnicity (4+1 v 5 black). We formalise this by summing over the four variables the numbers of participants with the same characteristics as this new recruit already in the trial:

Behavioural: 12 (sex) +7 (age) +4 (ethnicity) +14 (smoking) = 37
Nutrition: 11+5+5+12 = 33

Imbalance is minimised by allocating this person to the group with the smaller total (or at random if the totals are the same). Allocation to behavioural counselling would increase the imbalance; allocation to nutrition would decrease it.

Table 1 Baseline characteristics in two groups[4]

	Behavioural counselling	Nutrition counselling
Women	82	84
Mean (SD) age (years)	43.3 (13.8)	43.2 (14.0)
Ethnicity:		
White	94	96
Black	37	32
Asian	3	5
Current smokers	47	44

Table 2 Hypothetical distribution of baseline characteristics after 40 patients had been enrolled in the trial

	Behavioural counselling (n=20)	Nutrition counselling (n=20)
Women	12	11
Age >50	7	5
Ethnicity:		
White	15	15
Black	4	5
Asian	1	0
Current smokers	6	8

At this point there are two options. The chosen treatment could simply be taken as the one with the lower score; or we could introduce a random element. We use weighted randomisation so that there is a high chance (eg 80%) of each participant getting the treatment that minimises the imbalance. The use of a random element will slightly worsen the overall imbalance between the groups, but balance will be much better for the chosen variables than with simple randomisation. A random element also makes the allocation more unpredictable, although minimisation is a secure allocation system when used by an independent person.

After the treatment is determined for the current participant the numbers in each group are updated and the process repeated for each subsequent participant. If at any time the totals for the two groups are the same, then the choice should be made using simple randomisation. The method extends to trials of more than two treatments.

Minimisation is a valid alternative to ordinary randomisation,[2 3 5] and has the advantage, especially in small trials, that there will be only minor differences between groups in those variables used in the allocation process. Such balance is especially desirable where there are strong prognostic factors and modest treatment effects, such as oncology. Minimisation is best performed with the aid of software—for example, minim, a free program.[6] Its use makes trialists think about prognostic factors at the outset and helps ensure adherence to the protocol as a trial progresses.[7]

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BMJ 2005;330:843