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Avoiding bias in trials in which allocation ratio is varied

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Most randomised trials allocate participants equally to the interventions being compared – so the allocation ratio is 1:1 in a trial comparing two treatments. Sometimes an unequal ratio, such as 2:1, is adopted, and in some trials the allocation ratio is changed part-way through the study. In a recent trial of treatments for insomnia, for example, the allocation ratio was adjusted from 1:1 to 2:1 part-way through the trial to compensate for differential attrition.[1]

As Armitage and Borchgrevink[2] observed half a century ago, such a change is quite permissible. However, because not all patients in the total group had an equal chance of receiving each of the treatments, it is wrong to analyse the data ignoring the change in allocation ratio. Bias could arise if the participants enrolled in the two parts of the trial differed in important characteristics. A valid analysis thus requires the data for the two allocation periods to be analysed separately and the results then to be combined, as in a meta-analysis.

A similar issue arises when the allocation ratio varies between centres in a multicentre trial. In an unusual randomised trial, teetotal patients with diabetes were randomised to drink water or wine (150 mL) each evening with dinner, every day for two years.[3] The report of the trial is unequivocal: 'The two-year CASCADE trial involved alcohol abstaining diabetic participants who were randomly assigned in a parallel design (1:1:1) to mineral water, white wine, or red wine (150 mL at dinnertime)'. That sentence is admirably clear. But it is untrue. In fact, in this two-centre trial, participants in one centre and part of the other centre were randomised 1:1 to either water or red wine. The remaining participants in the second centre were randomised in a 1:3:1 ratio to drink mineral water or white wine or red wine. Hence, in fact, none of the participants was randomised 1:1:1 to one of the three drinks.

Again, it is not valid to analyse all the data as if this were a true three-group randomised trial, but that is what the authors did.[4] The comparison between water and red wine is entirely valid. But those patients allocated to white wine should have been compared only with those in the water and red wine groups who were randomly assigned in the same process, that is, only those in one centre in which a 1:3:1 allocation ratio was used.

A particular form of change of allocation ratio is when a treatment arm is added or dropped during the trial.[5] For example, a trial of the drug preladenant for patients with Parkinson's disease initially randomised patients to one of three doses of preladenant (1, 2 or 5 mg twice daily) or placebo.[6] Part-way through the trial, a fifth group was added and patients allocated to this received 10 mg of preladenant. The allocation ratio was changed from 1:1:1:1 to 1:1:1:2:1, with twice as many participants in the new high-dose group than in the other groups. As in the other scenarios discussed, between-group comparisons are valid only when restricted to participants who were randomised concurrently. In many such trials, however, the total dataset is incorrectly analysed, as if a fixed allocation ratio across all treatment groups was applied throughout the trial.

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