Economics notes

Use of unequal randomisation to aid the economic efficiency of clinical trials

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In an earlier note we showed how economic criteria can help in sample size calculations by defining clinical endpoints of economic importance.[1] However, there is a further issue concerning sample size calculations where economic information may be useful—the randomisation ratio.

Most randomised trials allocate equal numbers of patients to experimental and control groups.[2 3] This is the most statistically efficient randomisation ratio as it maximises statistical power for a given total sample size. However, this may not be the most economically efficient randomisation ratio.[4] When two or more treatments under evaluation have a cost difference it may be more economically efficient to randomise fewer patients to the expensive treatment and more to the cheaper one.

There are two economic issues related to randomisation ratios implicit within any trial. Firstly, when there is no limit to patient recruitment how can the statistical power of the study be maximised at least cost? Secondly, when there is a limit on total patient recruitment is the incremental cost of maximising statistical power worthwhile?

When there is no limit on patient recruitment the least cost study can be identified by estimating a total sample size assuming equal randomisation and then adjusting it by the allocation ratio determined using the formula[4]: $\sqrt{(Cost_{expensive}/Cost_{cheap})}$. This approach will, however, involve recruiting further patients, and the larger the randomisation ratio the greater the number of additional patients required. If the randomisation ratio, and hence the number of extra patients required, is large it may not be feasible to adopt the most cost effective randomisation ratio. However, substantial cost savings can still be achieved by adopting a smaller randomisation ratio, such as a ratio of 2:1, with only a modest loss in statistical power.

The table shows for two recent studies the likely cost savings if the trialists had adopted a randomisation ratio of 2:1—that is, for every three patients recruited two had been allocated to the less expensive treatment.[5 6] For large expensive trials unequal randomisation can yield large cost savings. For example, the two trials in the table would lead to a large reduction in costs with only a modest loss in statistical power.

Given that unequal randomisation is relatively simple to undertake and can lead to substantial cost savings, why is it not used more? One reason is that the savings of unequal randomisation (or the extra costs of equal randomisation) often do not fall on the budgets of research funders, so they have little incentive to consider these costs. Secondly, though unequal randomisation is well known to statisticians, few economists have realised the potential cost consequences of equal randomisation and even fewer are involved in designing trials. Thirdly, trialists often want to retain maximum statistical power, and the effort required to recruit the additional patients to ensure no drop of power is sometimes seen as not worth the cost savings.

Nevertheless, when experimental treatments differ substantially in their costs then for a given statistical power (assuming no constraints on recruitment of patients), unequal randomisation will produce the least cost trial. Therefore, when possible, unequal randomisation should be the method of choice when sizeable cost differences between the experimental treatments exist and there is no constraint on recruitment. When there is a ceiling on total sample size unequal randomisation can lead to substantial cost savings for only a modest reduction in statistical power.

1 Torgerson DJ, Campbell MK. Economics notes: Cost effectiveness calculations to aid sample size determination. *BMJ* 2000;321:697.
2 Moser CA, Kalton G. *Survey methods in social investigation.* London: Heineman, 1971.
3 Pocock SJ. *Clinical trials.* London: Wiley, 1983.
4 Torgerson DJ, Campbell MK. Unequal randomisation can improve the economic efficiency of clinical trials. *J Health Serv Res Policy* 1997;2:81-5.
5 Scandinavian Simvastatin Survival Study Group. Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian simvastatin survival study (4S). *Lancet* 1994;344:1383-9.
6 Chapuy MC, Arlot ME, Duboeuf F, Brun J, Crouzet B, Armaud S, et al. Vitamin D3 and calcium to prevent hip fractures in the elderly. *N Engl J Med* 1992;327:1637-42.

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Potential cost savings resulting from unequal randomisation

Trial	Treatment cost (and numbers) in expensive group of published design or assuming equal randomisation	Treatment cost (and numbers) in expensive group of modified design or assuming unequal randomisation	Cost saving	Changes in detectable difference	Change in power to identify original fixed difference
Published trials					
Scandinavian simvastatin study for preventing coronary heart disease[5]*	£4 448 641 (2221)	£2 993 101 (1481)	£1 495 540	30-32% difference in mortality	95% to 92%
Chapuy et al, Vitamin D and calcium for hip fracture prevention[6]†	£294 120 (1634)	£196 200 (1089)	£97 920	3.5-3.7% difference in fracture rate	90% to 86%

*Assumes an average use of 20 mg/day of simvastatin costing £31.09 a month for 5.4 years.
†Assumes two tablets daily of cholecalciferol (Calcichew D3 forte) at 1994 prices.