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Review

The use of unequal randomisation in clinical trials — An update

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ABSTRACT

Objective: To update a 2005 review of the reasons researchers have given for the use of unequal randomisation in randomised controlled trials (RCTs).
Main measures: Intervention being tested; type of study; number of participants; randomisation ratio; sample size calculation and reason given for using unequal randomisation.
Methods: Review of trials using unequal randomisation.
Databases and sources: Cochrane library, Medline and CINAHL.
Results: A total of 86 trials were identified. Of these 82 trials (95%) recruited patients in favour of the experimental group. Various reasons for the use of unequal randomisation were given including: gaining treatment experience; identification of adverse events; ethical; logistic and enhancing recruitment. No trial reported explicitly used it for cost-effectiveness. Most of the papers (i.e. 47, 55%) did not state why they had used unequal randomisation and only 38 trials (44%) appeared to have taken the unequal randomisation into account in their sample size calculation.
Conclusion: Most studies did not mention the rationale for unequal allocation, and a significant proportion did not appear to account for it in the sample size calculations. Unlike the previous review economic considerations were not stated as a rationale for its use. A number of trials used it to enhance recruitment, although this has not been tested.

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1. Background

Most randomised controlled trials (RCTs) aim to allocate equal numbers of participants to each trial arm in order to optimise the statistical power for a fixed sample size [87]. However, the use of unequal randomisation is on the increase [42]. There are a number of scenarios where it has been argued that the use of unequal randomisation can be advantageous.

1.1. Participant preference

Participant preference has been reported as a barrier to RCT participation [76]. Avins suggested that using unequal randomisation might increase the appeal of study participation [2]. However, a recent systematic review of interventions to increase recruitment rates did not find a trial comparing recruitment where participants were randomised to be offered equal or unequal allocation [89].

1.2. Ethical reasons

It has been argued that unequal allocation could be used for ethical reasons. Some view it as unethical to expose participants to side-effects or access to a potentially beneficial treatment but unequal allocation is advocated [2,17]. Thus, some may argue in instances where there is a 'no treatment' or placebo group that minimising the size of that group is advantageous for more patients. The issue here is that this presupposes that the researchers are not in equipoise and the smaller group is actually the inferior treatment, when this may not be true.

1.3. Learning curves

Some complex interventions may improve the more treatments a clinician delivers. For instance, in surgical interventions where surgeons may need to learn a new technique it could be useful to randomise more participants to the arm with the new treatment to allow more experience of the new technique resulting in a more precise estimate of the treatment and learning effects [85].

1.4. Cost

In some RCTs one trial arm will cost more than the other. Unequal randomisation allows more participants to be recruited to the least expensive arm or arms [86]. When a research budget is fixed but the sample size is not then more statistical power could be obtained by allocating more patients to the least expensive treatment and inflating the overall sample size until the budget is exhausted. For instance, if the sample size using equal allocation to identify a difference of 0.5 of a standard deviation were 64 in the intervention group and 64 in the control group we would have 80% power to detect a 0.5 difference. However, if resources were constrained to treating 64 intervention participants but there was no such constraint for the control patients then by using a 2:1 ratio (i.e., 64 intervention plus 128 controls) the power would be 90% to detect a 0.5 difference. However a previous review of unequal randomisation concluded that unequal randomisation was rarely used to confer financial savings [12].

1.5. Logistical reasons

In some studies it may be more logistically feasible to deliver an intervention using unequal allocation. For example, in studies comparing a group intervention to an individual intervention, where a group needs a certain number of people to make the group viable, it may be beneficial to randomise more people to the group intervention to allow adequate group sizes to be formed. For example in a study by Goodwin [21] which compared a psychosocial support group to educational materials for people with metastatic breast cancer, participants were randomised in a 2:1 ratio to the support group.

1.6. Statistical considerations

As noted above unequal randomisation will result in the maximum statistical power being achieved from a study where the sample size is not fixed but resources are [87]. However, there are some instances when it is anticipated that there will be post-randomisation differences in the treatment variance so that statistical power may be increased if more participants are allocated to the group with the anticipated larger variance.

Many of the issues described above were identified by Dumville and colleagues [12]. However, that review used a combination of electronic searches and personal knowledge so it may have been a biassed representation of the literature. In this updated review we have chosen to look for studies published since 2006 and used electronic search methods only.

2. Methods

The Dumville review searched the literature in four databases (Cochrane Library, Medline, PubMed and the Science Citation Index) from database inception to June 2005 and identified 65 RCTs which had used unequal randomisation [12]. The study was criticised for using limited search terms (these were: unequal or unbalanced, randomis(z)ation, allocation or ratio) which, it was suggested, may have meant that a number of relevant studies using unequal randomisation were missed [54]. In this current review we undertake an updated and contemporary review on the use of unequal randomisation since 2005 using a revised search strategy. Furthermore, the previous review also included studies known to the authors, but which were not necessarily easy to find through electronic searching. We aimed to investigate the prevalence of unequal randomisation in published studies from 2005 to 2014 and describe the types of studies using this approach and the reasons for its use as well as any disadvantages observed.

Unlike the previous review we did not supplement the electronic search strategy for RCTs known to the review authors. This would allow us to get a representative sample of the published trials.

2.1. Included studies

We aimed to include two arm RCTs that had used unequal randomisation in a ratio of 1:2, 1:3 or 2:3 and which were drug trials, surgical trials, trials of devices, and trials of complex interventions (interventions with several interacting components such as acupuncture [10]).

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