CLINICAL TRIALS

A Place for Randomization in the Interval Between the End of Recruitment and Availability of Results

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Abstract

There is a time delay between the final recruitment of patients to a randomized controlled trial and the publication of results. The practical options available to decision makers during this gap can be listed according to whether all treatments are already widely available or whether at least one has been restricted to the trial. When the treatments are already in widespread use, the options are simply either to stop randomizing or to continue. When one trial treatment is restricted, there are further options: a) withdraw the restricted treatment altogether, pending the final analysis; b) continue to offer randomization, with a view to providing further data should these be needed; or c) make the intervention widely available to patients who would have previously been eligible for the trial. In this paper, we discuss the relative advantages and disadvantages of each option and discuss their attendant ethical implications. In particular, we suggest that continuing randomization is an option worthy of serious consideration. Randomizing patients acts as a "hedge" against the need for more data, given that sample size calculation is an inexact science. However, patients must be made aware of the basis on which randomization is offered.

Keywords: Randomized clinical trial, Sample size, Recruitment, Ethics

THE PROBLEM

There is a time delay, sometimes a very long delay, between the final recruitment of trial patients to meet a planned sample size and the publication of its results. Because there are several different ways of proceeding during this delay, there is a decision to be made over what to do during this "gap" period. The problem is most pressing when planned recruitment is completed in a much shorter time period than the individual follow-up times for outcomes. Here, we address this problem in the context of interventions that are one-off treatments with extended follow-up, leaving aside trials of ongoing treatments. An example, which recently needed resolution in the United Kingdom, was laser-assisted revascularization of the ischemic myocardium.

The decision is best made just before the gap; the decision makers will typically be the trial sponsors, who will be advised by others, such as the trial steering committee. The gap problem can be foreseen at the design stage, and funders and ethics committees should make it an explicit part of each trial protocol, with provision for dealing with it as and when it arises.

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DECISION OPTIONS IN THE GAP

The practical options available to decision makers can be listed according to whether all treatments are already widely available or whether at least one has been restricted to the trial. This distinction has implications for the relative advantages and disadvantages of each option, both scientifically and from the perspective of individual patients.

When the treatments are already in widespread use, the options are simply either to stop randomizing or to continue. When one trial treatment is restricted, there are further options:

- *Option 1*: Withdraw the restricted treatment altogether, pending the final analysis;
- *Option 2*: Continue to offer randomization, with a view to providing further data should these be needed; or
- *Option 3*: Make the intervention widely available to patients who would have previously been eligible for the trial.

ADVANTAGES/DISADVANTAGES OF EACH OPTION

Where the Trial Treatment Is Already Widely Available

When all treatments are already widely available, the only advantage to pursuing randomization may be the "insurance" it offers against setting the sample size too small at the design stage and being left with too imprecise a result. Sample size calculation is far from an exact science (2;5). It is not uncommon for trialists and funders to be unhappy with the precision of the estimates of relative effects of comparator treatments. This may be due to: a) unexpectedly large variability in the continuous outcome; b) an unexpectedly low failure rate for a binary outcome; or c) a difference in the effects of the two treatments being smaller than had been (over-optimistically) expected, thus requiring greater precision to indicate reliably whether one treatment is truly a worthwhile improvement on the other. The last reason is perhaps the most common. A trial may yield a precise estimate of effect along one dimension (for example, cost or well-being) but may fail to do so for other outcomes, typically death rates, against which the short-term outcomes may have to be traded-off. Even if sufficiently precise estimates were achieved overall, there may still be imprecise estimates in certain crucial subgroups.

If randomization is to proceed during the gap, it could be used to collect a restricted, less expensive set of outcome measures or simply to enable collection of outcomes at a later date, if required. The decision to "activate" (that is, collect and analyze) insurance data would be based on the analyses of the main data set. This will not worry Bayesians, but frequentists, who concentrate on testing a null hypothesis, will worry that this will increase alpha (i.e., the risk of getting a type 1 error or false positive result). A statistical adjustment, akin to those used for multiple analyses of data without increasing alpha, would be needed.

Where the Trial Treatment Is Restricted to the Trial

However, when one of the experimental treatments has been restricted to the trial up to that point, the situation is more complex. We will deal with the options in turn, presenting relative advantages first and disadvantages second.

Withdraw the Restricted Treatment Altogether. This option has many disadvantages:

- Where the experimental treatment requires skill and expertise to administer, these may be lost during the gap, so if the experimental treatment proves superior, it may be more difficult and costly to make it widely available later;

- In any case, if an experimental treatment is difficult and expensive to install, yet has relatively small operating costs, it may make little sense to leave it standing idle, even if, in the end, it is decided that for economic reasons, it cannot be installed more widely; and
- Clinicians and patient groups may feel aggrieved at having a treatment option withdrawn.

Continue to Randomize and Register Patients with a View to Data Collection and Analysis If the Need Arises Later. This option has not seemingly been discussed in the literature despite its being worthy of serious consideration.

Advantages are:

- Skills would be maintained and expensive equipment would not stand idle, giving it an advantage over option 1;
- Costs would be limited (compared with option 3);
- Its main advantage, over all the other options, is that it would provide, at relatively low cost, extra data in the event that the results of the main trial are insufficiently precise (the "insurance" principle); and
- Continuing to provide the treatment only for research purposes may provide a logical and defensible basis for resisting any consumer pressure to make it widely available.

Disadvantages are:

- Costs could be considerable;
- The Health Service may be accused of using extended randomization as a pretext for denying wider access to the treatment, especially if the likelihood of a research dividend is small; and
- The extended use may make later withdrawal more difficult if the trial come out negative.

Make the Intervention Widely Available to Everyone Within the Trial Area in Anticipation of a Positive Final Result. Disadvantages are:

- Costs would be considerable;
- The question of why a randomized controlled trial (RCT) of a restricted treatment was funded in the first place arises if the experimental treatment could be made available at this juncture, assuming no other convincing data emerged in the interim;
- It could be difficult to hold the line and restrict the treatment to communities previously included in the trial; and
- Withdrawing the experimental treatment would be more difficult if this proved necessary.

ETHICAL IMPLICATIONS

With respect to research trials, it is widely acknowledged that participants should give their informed consent and they should not lose out by participating compared with what they could expect to get routinely (1). This means that they should be in equipoise or better between trial arms and all other available alternatives. However, some patients may include a measure of altruism in their evaluation of equipoise, i.e., they are prepared to suffer some inconveniences and even some loss of physical health to help others.

If randomization were to be used during the gap for research "insurance," it would be important that participants knew that their data might not contribute to the future welfare of others. Under these circumstances, altruistic patients may well be less likely to consent. Even during the main phase of an RCT, there is no guarantee that a particular person's data

will contribute to the future welfare of others (e.g., if the trial "question" is made irrelevant by developments elsewhere) although under most circumstances it would be analyzed. The essential point is that patients should have a reasonable idea of the probability of their data being used and how it might contribute to society.

FUNDING ISSUES

If randomization in the gap is used primarily to gather insurance research data, then the research funder should underwrite the extra research costs during the gap. In the United Kingdom, the net excess treatment costs would normally be met by the health service concerned, but this will vary from country to country. However, if randomization is continuing partially because the health service wishes to maintain expertise or wishes to avoid monetary or political costs, then the health service should also meet some of the research costs. The different reasons for continuing to fund in the gap may lead to confusion of responsibility about these obligations. This is further argument for thinking about the gap at the protocol or funding stage. Some flexibility may be required in deciding whether to collect and analyze follow-up data from patients recruited during the gap. This flexibility is a desirable feature of trial funding more generally (3;4).

CONCLUSION

For some trials, there is clearly a complex decision to be made about the gap between final recruitment and the results. The various options do not appear to have been previously recognized or discussed. "Insurance" randomization is likely to be more important when follow-up times are long compared with the total period of recruitment when skills would otherwise decay, when expensive equipment is underused, or where there is consumer pressure for wide provision of a treatment restricted to the trial. If nonresearch considerations appear important, funders should consult an agreed health service contact for initial discussions and, if applicable, agree on a provisional plan with estimates of costs and to whom they would apply. Making these issues clear in the protocol would ensure that funders were not seen to be prolonging randomization purely in the hope that a favorable result will eventually emerge.

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