Can unequal be more fair? A response to Andrew Avins

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Abstract
In this paper, we respond to Andrew Avins’s recent review of methods whose use he advocates in clinical trials, to make them more ethical. He recommends in particular, “unbalanced randomisation”. However, we argue that, before such a recommendation can be made, it is important to establish why unequal randomisation might offer ethical advantages over equal randomisation, other things being equal. It is important to make a pragmatic distinction between trials of treatments that are already routinely available and trials of restricted treatments. We conclude that unequal randomisation could, indeed, be an ethical compromise between protecting the interests of participants and those of society.

Keywords: RCTs; human experimentation; ethics

Introduction
In the context of randomised controlled trials (RCTs), there can be an ethical tension between the best interests of society at large and the best interests of the individual participants. A tension exists if individuals are called to sacrifice their best clinical prospects by participating in trials for the common good.1–3 In his recent article, “Can unequal be more fair? Ethics, subject allocation and randomised clinical trials”, Andrew Avins4 reviews five existing, though not necessarily established, methods which could be used in clinical trials to make experimenting with human subjects more ethical: unbalanced randomisation; adaptive randomisation; sequential design; adjusting the overall significance level; and Bayesian techniques.

We would like to respond to his analysis of the first of these methods, namely, unbalanced or unequal randomisation. This method gets its name from the number of trial participants who are allocated to the intervention against the number allocated to control. The proportion of trial participants getting the intervention is called the randomisation ratio. This ratio is usually 1:1, assuming only two trial arms, ie an equal proportion of participants get one treatment as get the other. Unequal randomisation simply means that more than half of the trial recruits will be allocated to one of the trial arms. We will assume for present discussion that the randomisation ratio is set at the outset and constant throughout the course of the trial. Some of the following issues also relate to what is called the “adaptive design”, where the ratio changes in line with accumulating data. This method creates further ethical issues, such as keeping interim data secret, so we will not pursue it here.

We have isolated unbalanced or unequal randomisation for further analysis, because Andrew Avins’s review gives it more weight and attention than the others, but his review falls short of providing much in the way of structured analysis. It concludes with a strong recommendation that investigators should be actively encouraged to think about designing trials using unequal randomisation as a way of making their experiments more ethical and that ethics committees should not reject outright protocols that propose unequal randomisation. While we agree that there should be more awareness of unequal randomisation, we do not share Andrew Avins’s blanket enthusiasm for it. With the benefit of further analysis, we show that it might, indeed, confer benefits on participants of trials and we show why. Our analysis is based on an established ethical framework, which can be applied to research trials generally.

Research ethics
It is perhaps most useful to limit our discussion to ethical ideas which stem from two moral traditions, namely, utilitarian and Kantian ethics. As regards the utilitarian doctrine, rational individuals usually seek to maximise their own expected utility and should be allowed to do so, unless there is some judicial reason to limit their individual liberty.5 This premise is sometimes called the “expected utility” rule. When applied to trials
generally, we can say that, given pre-trial knowledge, recruits should not expect to lose out by entering the trial. Obviously, a new drug’s costs and benefits are not precisely known at the time of trial recruitment or the experiment would not be taking place. But more generally, doctors and patients cannot usually predict for sure how a particular treatment will work on a particular patient, even after a trial has taken place. As Avins points out, we thus have to make decisions under uncertainty, using degrees of knowledge about their consequences. Decision theory provides just such a mechanism. Rather than ignoring uncertainty (which is what sometimes happens in routine practice), the extent of uncertainty can be explicitly taken into account.

Kantian ethics, briefly, says that we should respect a person’s autonomy. Applying this to trials, it means that individuals can choose freely whether they participate or not. Utilitarian and Kantian traditions are not necessarily incompatible, as fully-informed and autonomous individuals are usually best placed to maximise their own expected utility.

Expected utility of a trial relative to routine care

The defining feature of a RCT is the way in which treatments are allocated. In medical practice, patients simply choose which of the available treatments they want and so have a 100% chance of getting their preferred treatment, assuming, of course, they have a preference. In randomised controlled trials, the situation is different in that each participant has a probability, which is less than unity, of receiving one or other trial arm.

Where Avins’s review falls short is that it does not carry through a pragmatic distinction between those circumstances in which the trial treatments are already freely and routinely available and those in which the trial treatment is restricted to the trial and is consequently not available on a routine basis. Roughly speaking, when a trial treatment is routinely available, patients who prefer it can simply opt for it, whereas if it is restricted to a trial, they cannot. In this paper, we assume that the circumstantial distinction between treatments that are already widely available and treatments that are restricted for research purposes is a clear distinction and is also exhaustive. However, in practice, we recognise that this is not always the case. Some treatments that are primarily part of a research programme may also be partially, though not entirely, available to the community at large. Some trials seek to evaluate treatments that are already used on a routine basis and so are to all intents and purposes as widely available as they will ever be.

1. When trial treatments are already freely and routinely available

When a trial treatment is already freely and routinely available, a fully-informed and rational patient following the mathematical “expected utility” rule will only consent when she perceives no positive net difference between any of the available treatments and each of those offered in the trial. In this case, she can be said to be in a state of “equipoise”. Participants do not expect to lose out from entering the trial. Andrew Avins points out that, when equipoise applies, there is no a priori reason why the randomisation ratio should be set at 1:1. That is, there is nothing to say that the same proportion of patients should be allocated to the experimental arm as are allocated to the control arm. Given equipoise, it does not matter from the participants’ perspective what ratio is set, so maximising information from the trial (and hence benefit to future patients) should be the prevailing concern.

Given equipoise, participants may be altruistic in the weak sense that they are actively consenting to randomisation instead of passively accepting a default treatment. Avins recognises that, in practice, many patients will prefer one or other treatment and so will not be in equipoise anyway. This may not prohibit ethically acceptable recruitment, as some patients may be strongly altruistic, i.e. they may be prepared, or actively wish, to sacrifice a degree of expected clinical benefit from treatment for the satisfaction of helping others. This degree of altruism could, indeed, be included formally in the decision making process above along with any other patient-specific factors, so that anyone agreeing to randomisation would not, by definition, lose out in prospect, notwithstanding any treatment preferences. It is worth noting that the degree of altruism necessary before trial entry becomes an acceptable option for a rational patient, would vary according to the ratio of randomisation. That is to say, the bigger the chances of getting the preferred treatment, the less would be the altruism required. It is not outside the realms of possibility to offer patients a choice of ratios, where possible, maybe just equal for the very altruistic or unequal for the not so altruistic (or, the treatment routinely, of course, for the self-interested), and let them decide on an individual basis. Increased choice of ratios may correspondingly increase recruitment to the trial. Going down this line would make analysis increasingly complicated and, given that the average patient has difficulty understanding the very concept of randomisation, a well-meaning attempt to increase patient choice by offering different ratios may only serve to confuse.
In short, compared with equal randomisation and ignoring altruism, unequal ratios have nothing to offer in the way of protection for trial participants when the trial treatments are already freely available (and are, in fact, offered to patients). Participants may have more or less chance of getting their preferred treatment but this chance would still be less than the certainty they would have had by not entering the trial at all. Some patients who would not enter a trial with equal ratios could find a trial with unequal ratios more attractive and so the trial could recruit more easily.

2. When trial treatments are restricted to the trial
We now move onto the very different situation where a trial treatment is only available within the confines of a trial. Patients who would have entered the trial, if it had been set up as a trial of widely available treatments, should still enter. But these are not the only patients who could rationally agree to be randomised. Indeed, a fully informed and rational person could consent to randomisation because she prefers a restricted treatment that is not available routinely. A preference may be based on expectation in light of existing data or on hope in the face of limited options. It is worth stressing that any pretrial preference is couched in uncertainty and may turn out to be a bad choice in fact. Equal randomisation, under these circumstances, would mean that patients would be offered a 50% chance of getting their preferred treatment by going into the trial rather than no chance of getting it at all by adopting what is then routine. Unequal randomisation might mean that they would have a greater than 50%, but less than 100%, chance of getting this treatment.

There could still be an ethical tension between giving individual participants only a 50% chance of getting their preferred treatment when they would really have liked to select it routinely even with uncertainty. But this is primarily part of a more general question about restricting treatments to trials in the first place and not about what randomisation ratio should be used, given certain restrictions. New treatments could be restricted by a central authority, for example, pending full evaluation of cost-effectiveness. Indeed, there is a spirited debate in the literature concerning what to do when there is a widespread and very strong preference for a new treatment. This debate has not really focused on randomisation in unequal ratios—with a few notable exceptions—but so much as whether restricting access is justified at all. If made widely available, such treatments would not undergo proper evaluation, but, if restricted, some patients, desperate to try anything because there is no existing standard treatment and their medical condition is life-threatening, will not get the medical help they need. Such patients may have nothing to lose and everything to gain.

It is clear that randomisation in unequal ratios might be worth considering as an ethical compromise between full access and restricting new treatments in a trial recruiting patients equally to that treatment and to control. It is a compromise because it may be a better, if not perfect, solution from the self-interested participants’ perspective and will provide some comparative data! For those patients who do not want to go into the trial, they can still opt for any routine treatment, assuming there is one. The ratio of randomisation would still have to be set and it would be important to provide a sufficient number of randomised patients on the routine treatment arm to yield useful results. In addition to getting a better chance of being allocated to the restricted treatment, a trial with an unequal randomisation ratio in favour of that treatment could increase the size of any placebo effects experienced by the patient. This is because he would believe more strongly that he is getting his preferred therapy through informed consent and he does not know for sure which trial arm he is on, i.e. blinding is secure.

There could be other reasons for using unequal ratios besides attempting to protect the best interests of trial participants under restrictive circumstances.

One reason for using unequal ratios is a scientific one: to gather more information on important, yet relatively uncommon, “side effects” of a treatment by randomising more patients to it. More patients might be allocated to the treatment with suspected side effects of interest than to another without. This could only be achieved at the expense of precision estimates on primary outcomes. In addition financial restrictions could mean that investigators might want to randomise patients unequally, resulting in more getting cheaper treatments and fewer getting expensive ones. The ethical desire to randomise unequally in favour of a new, expensive and preferred treatment might run counter to financial inclinations to do precisely the reverse. If a trial, randomising unequally to satisfy financial constraints, were the only way to make an expensive therapy available, admittedly only to a few randomly selected patients, then ethics committees should not reject such a protocol on the basis of its randomising unequally alone. But if the preferred therapy could reasonably be made more available, through randomising equally or unequally but in favour of the preferred treatment, then ethics committees could insist on this before a trial goes ahead. This could mean that more patients are recruited to
a trial, given a fixed amount of an expensive and preferred treatment, and a larger number of patients are likely to experience placebo effects associated with a belief that they may get their preferred therapy. The placebo effects, while experienced by more people, would in all probability be diluted in relation to those expected in a trial with equal ratios, because the chances of getting the preferred treatment are smaller.

Voluntary decision making
The amount of choice competent individuals can exercise will, as with their expected utility, depend, in part, on the circumstances in which a trial is mounted. We will discuss the implications of the two scenarios above with respect to voluntary choice.

Where the intervention is already widely available
Competent participants can choose voluntarily to go into a trial or to select the intervention, provided they are in charge of all the relevant information, are not deceived, and are not coerced. Whether equal or unequal randomisation is used does not obviously impact on the voluntariness of a person’s decision. However, if unequal randomisation were used to deceive patients into thinking they had the best chance of getting their preferred treatment by going into a trial when in fact they could get hold of it routinely, then their ability to make a free and informed choice would be under threat. Unequal randomisation has been used on occasion with a mind to increasing recruitment. Such sleights of hand would be using people solely to increase recruitment and would, as such, be unethical.

When treatments are restricted
A patient’s ability to choose freely may be in question even when he is availed of full and accurate information. However, the ratio by which patients are randomised does not make any difference to the number of choices available to patients once a restriction has been enacted. Offering a number of different randomisation ratios would be preferable, but not doing so would not seem to infringe autonomy, only put limits on it.

Conclusion
Randomisation in unequal ratios does go some way to resolving ethical tensions between the interests of individual participants (and maybe even increasing the number of participants who might benefit from a trial) and the interests of society and of future patients. Given that patients are not altruistic and given that a trial treatment is already routinely available, either a patient is in equipoise in which case any randomisation ratio is just as good prospectively) or a patient has a preference for one of the trial arms and can choose that treatment regimen outside the trial irrespective of the randomisation ratio. However, patients could have varying degrees of altruism and some may be prepared to go into a trial with unequal ratios while not being happy about going into a trial with equal ratios. Recruitment is thus likely to be increased by accommodating these patients and using different ratios.

When a trial treatment can only be accessed by going into a trial, unequal randomisation may increase the patients’ expected benefit from going into a trial when it increases their chances of getting the treatment they want. Even if the ratio of randomisation is set so that fewer patients get a preferred yet untested treatment than get a control, more patients may reap benefits from placebo effects associated with the knowledge that they may be getting that treatment.

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