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Commentary

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Abstract

In this commentary on Fries and Krishnan's argument that 'design bias' undermines the status of equipoise as the ethical justification for randomised controlled trials, it is argued that their argument is analogous to Bayesian arguments for the use of informative priors in trial design, but that this does not undermine the importance of equipoise. In particular, mismatches between the outcomes of interest to industrial sponsors of research and outcomes of interest to patients and clinicians ensure that in many cases industry-sponsored trials can fail to reflect the reasonable equipoise of working clinicians.

Keywords: design bias, ethical principles, expected outcomes, randomised controlled trials

Introduction

James Fries and Eswar Krishnan have recently presented an interesting argument for the proposition that 'equipoise is a false and diverting principle' and propose an alternative test of the ethics of a randomised controlled trial, the 'positive expected value' test [1]. The concept of equipoise has been introduced into the medical literature on many occasions [2–7]. Both concepts are intended to give ethical justification to entering patients into randomised controlled trials. The problem that critics of such trials pose is that entering a patient into a trial seems to involve knowingly failing to offer the patient the treatment the doctor believes to be best for the patient, in the interests of scientific research and future patients. However, if there is genuine uncertainty as to which of the treatments being compared is superior, then randomised assignment can be justified [8]. There is considerable debate in the literature about how to give rigorous expression to what 'genuine uncertainty' requires. How much uncertainty? Whose uncertainty? When should we stop being 'uncertain' and start being 'certain'? The concepts of 'equipoise' defined in this literature are all attempts to give more precise expression to what is meant by 'uncertainty' here, and to give a sound basis to the ethical justification of randomisation in controlled trials.

Design bias

Fries and Krishnan argue that in the context of licensing trials of new drugs these debates are irrelevant and misleading. They argue that new drugs that reach industry-sponsored phase III trials are more likely to be effective than not, because they reach this stage of testing only if they have survived rigorous preclinical and clinical screening, and because the trial design decisions that are taken are those most likely to produce a positive result. They argue that this is demonstrated by the fact that all the trials they reviewed produced positive results in favour of the new drugs being tested [1]. On the basis of this, they argue that equipoise is being systematically violated.

Their empirical argument is not strong methodologically, and they acknowledge that there are alternative explanations for their finding. In addition, their *ex post* finding that all the trials they reviewed gave positive results does not entail that *ex ante* the triallists were not substantially uncertain that they would gain a positive result. Nevertheless, their qualitative argument for the existence of 'design bias' is plausible. The question is: what follows from this?

Design bias and the Bayesians

One response is to argue that the Fries–Krishnan argument is nothing new, because in effect the Bayesians have been arguing something similar for years. Some Bayesian philosophers argue that randomisation is unnecessary in the first place, and on that basis randomised controlled trials are unethical [9,10]. Most Bayesian statisticians and triallists, however, do accept that randomisation has its place in trial design [11,12]. What is required, they say, is that one starts with an 'informative prior' that fixes the rate at which people are initially randomised to different arms of the trial. On this account, something like equipoise or uncertainty remains the ethical justification for randomisation. The concepts of equipoise normally used are qualitative (one is either uncertain, or not, or the community at large is uncertain or not). Here the concept used is quantitative (one specifies a degree of belief in the proposition that the new drug is safe or effective, and a range of degree of belief within which one is 'uncertain' as to the truth or falsity of that proposition) [13].

As Fries and Krishnan argued, and as most Bayesians also accept, this approach to the decision to run a trial, and to design in it a particular way, involves subjective judgements about what is important and about what it is fair to offer patients. This then involves placing weight not only on what clinicians believe, and on what they think is important, but also on what patients believe and think important [5,14,15].

Problems with the Fries–Krishnan–Bayesian approach

One response to the claim that phase III trials are systematically prone to design bias is the following. Suppose that any new drug in phase III trials is likely to work, at least to some extent. The primary purpose of such a trial cannot then be to determine whether or not the new drug is effective. Instead, it is to measure how effective it is, and, secondly, to identify any problems with using the drug in clinical practice (rare adverse events, the tolerability of known side-effects, adherence to treatment, quality-of-life issues). If this is the purpose of phase III trials, then this will mean that different types of design and different numbers of patients will be required in many cases than are now required for trials that aim at proving effectiveness alone. This may have the effect of undermining 'design bias'. If the origin of design bias is sponsors selecting the design that will put their new product in the best light, then this represents a constraint on the designs they are entitled to choose.

Developing this, admittedly speculative, thought, even within the Bayesian approach there is considerable complexity. Designs that make full use of the ability to alter the assignment of patients to arms of the trial in the light of new information can be complex and difficult to analyse, and the choice of prior to reflect the different degrees of belief of sceptics or enthusiasts in the clinical and patient communities can be controversial [12,13,16]. Designing a trial that reflects the triallists' confidence in the new product, while allowing a fair test of that product, which produces results that can be understood by, and can hence persuade, the clinician who is neutral about the new product is harder than it looks. Fries and Krishnan might object that if design bias is endemic, then the clinician ought not to be neutral about new products; this is a very strong claim to make, however, and I will return to it.

The next problem is that a design chosen to present the new drug in as favourable a light as possible may well not be the design that answers the question that is clinically relevant [17]. They may measure the 'wrong' outcomes or make the 'wrong' comparisons. Clinicians may be interested in the relative effectiveness of drug versus surgery for osteoarthritis of the knee, yet they are offered very little evidence on this type of question; patients may be more interested in mobility than in pain control, but mobility may not be used as an outcome measure [18,19].

Consider, therefore, the clinician who is not involved directly with the drug development but is interested in either participating in the trial, or (later on) in using the results of the trial to inform her practice. On the Fries–Krishnan view, she ought to have a prior degree of belief in favour of the new product's effectiveness. Other things being equal, she seems to be being asked to consider any new drug as an advance – otherwise why would the drug company put all its effort into developing it? Yet the reasonably experienced clinician will know that new drugs are not always advances on the existing pharmacopoeia, will not always give patients outcomes they prefer, and may sometimes be harmful or ineffective in practice. So how enthusiastic ought the clinician to be? The reasonable patient deserves to be informed by his clinician about new products and new trials, but also about the ins and outs of such products and such trials. In practice, these considerations would lead clinicians and patients towards something very like equipoise, save in those happy situations in which there is close concordance between the interests of patients, clinicians, triallists and sponsors.

Conclusions

Fries and Krishnan are certainly correct in arguing that the equipoise concept has serious problems. Yet it is not the case that it is dead in the water. For practical clinical purposes it remains the central test of the ethical justification for randomisation. They are also correct to stress the role of patient autonomy and patient preferences in the design and conduct of trials. What they establish is that equipoise is neither a necessary nor a

sufficient condition for a trial to be justified. Some trials do not require equipoise, and not all trials with equipoise are ethically justified. For example, phase I and II trials are rarely based on equipoise, and some trials in chronic illness or in non-serious acute illness can be conducted with placebo control even when there is an effective standard therapy, provided that the patients consent and are really free to choose the alternatives [20]. Some trials of potentially life-saving treatments, to which there is no effective alternative, are arguably unethical if patients have no choice but to enter the trial [21]. Patient autonomy is surely very important.

But the point of the equipoise principle is that doctors need to be able to assure themselves and their patients that the offer of randomisation is not suboptimal. The defect of the Fries–Krishnan claim (that trials can be ethical if there is positive expected benefit) is that this need not be maximal: doctors, on this theory, can knowingly and willingly do less than their best for their patients. The point of the equipoise theory was that it seeks to show how randomisation can be consistent with seeking to do one's best for one's patient. Although conceptual problems remain to be resolved with equipoise, the ethical costs of giving up on it as the default justification are high [4,5,7]. It may be that we will eventually find a better justification for trials than equipoise, but I am not convinced that 'design bias' is a sufficient reason to give up on equipoise just yet.

Competing interests

The author declares that he has no competing interests.

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