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Education and debate

Ethics of clinical trials from a bayesian and decision analytic perspective: whose equipoise is it anyway?

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Should the equipoise of the patient, or that of the doctor, determine whether a patient enters a clinical trial? People asking patients to consent to trials are glossing over the ethical complexities. Choices should be based both on probabilities of events (which experts might know) and on the value that a patient places on those events (which only the patient can know)

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A recent systematic review of the ethics of randomised clinical trials shows that they are often justified on the basis of the uncertainty principle.[1 2] The central idea is that people contribute to posterity at no cost to themselves, if the "best" treatment is "unknown." This idea has been used to describe the scientific case for trials and to guide informed consent when individuals are invited to participate. Two examples illustrate this. The United Kingdom's Central Office for Research Ethics Committees suggests the following wording for information leaflets given to the participants of trials: "Sometimes because we do not know which way of treating patients is best, we need to make comparisons."[3] Donovan et al recently described factors affecting recruitment to a randomised clinical trial of active monitoring, radiotherapy, and radical prostatectomy and "found it necessary to emphasise that recruiters must be genuinely uncertain about the best treatment, believe the patient to be suitable for all three treatments, and be confident in these beliefs."[4]

In both cases the concept that the best treatment is unknown, which properly explains why a trial is worth doing, is carried over into the invitation to participate. Here I argue that such language, while providing the scientific and social rationale for trials, is inadequate—indeed misleading—when used to suggest that a patient might participate at no personal cost. This is because the words "best" and "unknown" are far too imprecise to properly inform choice.

Best treatment—a question of values

Treatments typically influence competing objectives. Radical prostatectomy versus more conservative methods, for example, involves a trade-off between cure and side effects. Because different people value outcomes differently, the best treatment can only be determined after an individual has been consulted in such a way as to invite careful consideration of the issue. Donovan et al advocate that men be informed unequivocally that all treatments for early prostate cancer are equally suitable, but this does not encourage individuals to explore their values in such a way that these can be reflected in decisions taken. A man with early prostate cancer who wants a child may place a higher value on preservation of fertility than someone who has no such aspirations. So, given a typical decision involving trade-offs, a recruiter cannot legitimately be uncertain about the best treatment until the individual concerned has been consulted. Stating unequivocally that the best treatment is uncertain, as advocated by Donovan et al, forecloses on further discussion about which treatment may best suit an individual. Indeed these authors go on to say that "if recruiters gave any indication that they were not completely committed to these aspects, patients would question randomisation, often using subtle and sophisticated reasoning." So, confidently stating that the best treatment was unknown would suppress sophisticated questioning. Provided no one spots what is going on, trials are likely to flourish but at the cost that patients will not be put in the best position to choose their care. The conclusion that the best treatment is unknown is a possible result of a patient's decision, not an input to that decision.

Different meanings of "unknown"

"Unknown" or "uncertain" literally means not known or not certain. This is not, however, equivalent to saying that all possible effects are equally likely, since knowledge is not dichotomous but accrues by degree. Some evidence always exists before a randomised clinical trial is done: in vitro and animal experiments, the same treatment in other diseases, similar treatments in the same disease, and perhaps even randomised clinical trials done elsewhere. Thus clinicians have some idea of what treatments might accomplish, even in advance of a trial. Saying that an effect is unknown leaves the extent to which it is unknown quite unclear; effects of two different treatments may be unknown, but the effects may be more certain in one case than in the other. Thus a patient may interpret unknown to mean that the recruiter has no idea at all, when the recruiter might mean unknown in the literal or the statistical sense.

Moreover, unknown gives no idea of how the problem is bounded. In the case of early prostate cancer the potential mortality gain from radical prostatectomy is bounded by the upper plausible limit on the

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proportion of prostate cancers that progress. To cover all this up under the blanket term of unknown may leave the patient thinking that there is nothing known, as opposed to less known than there will be after completion of the trial. The fallacy of dichotomising knowledge into known and unknown is inherent in bayesian statistics, where the probabilities of treatment effects before a trial is reported (prior probabilities) are graded on a continuum, ranging from the best guess, through effects of progressively lower probability, to end in those considered implausible.[5–8]

Prior probabilities and the ethics of inviting people to be randomised

The formal method for combining values and bayesian probabilities is decision analysis, and it is used to calculate which treatment maximises welfare or expected utility.[5–11] If the prior probability that radical treatment would improve mortality from prostate cancer was 5 percentage points, then a man who was particularly apprehensive about side effects (for example, a newly married man who wanted to have a child) might be better off with conservative treatment, whereas another (one, perhaps, who no longer placed a high premium on his sex life) might gain most from radical surgery. However, the losses and gains might balance for yet another man, both treatments having equal expected utilities, and such a person can accept randomisation without loss—he is equipoised.

How can patients get a prior sense of the effects of treatments—that is, of prior probability? Some patients might wish to adopt their caregiver's best prior whereas others might wish to be party to previous salient research and so adapt their caregiver's prior or form a prior entirely of their own. Caregivers need to ensure that patients understand that a prior is a personal best guess and that there are other opinions, but clinicians or patients always have to make inductive judgments about the likely effects of treatment in an individual case, taking into account factors such as grade and stage of tumour and the patient's age. The fact that clinicians vary in their opinions or that some may be more knowledgeable or experienced than others is no more germane to trial practice than it is to non-trial practice. In both cases the clinician should seek as fair a portrayal of the evidence as possible. The blanket term of unknown sidesteps any indication of the magnitude of possible effects, reducing the chance that potential participants will be able to appreciate what is really at stake.

Some potential participants might also be prepared to sacrifice an element of personal gain to help others, in which case, provided they are fully informed in the first place, they can factor the perceived advantages of altruism into their decision. Altruism is the patient's prerogative, which cannot be exercised if values and prior probabilities are all subsumed within the unknown. Some patients may be unable to give consent or may wish to abrogate the decision to their caregiver. In that case, unless a relative or close friend believes otherwise, the patient should be assumed to have average values. For clinicians who consider themselves to have average values, the relevant question is "How would I wish to be treated in the circumstances?"

Maximising recruitment versus full disclosure

Greater disclosure seems to reduce recruitment but increase understanding; being more explicit about what is at stake seems to prompt people to select one of the treatments on offer and to eschew randomisation.[1 12] The unqualified phrase "the best treatment is unknown," when used to solicit entry in randomised clinical trials, is thus a procrustean device which seeks to make all comers fit trial requirements. So, which is most important; promoting understanding or maximising recruitment?

Empowering choice will be given precedence by those who, like me, think the obligation to respect individual autonomy outweighs the common good in all but the most extreme cases (war or driving with epilepsy, for example). This conforms with Kant's injunction that people should not be used as a mere means to an end. Even utilitarians may agree that facilitating individual choice is more important than maximising recruitment (at least in the context of unrationed treatments), because patients may vote with their feet if they see through the subtle coercion to participate in randomised clinical trials inherent in the use of culpably obscurant language.

Lastly, much is made of the putative trial effect, whereby patients may fare better in trials, net of any benefits intrinsic to treatment in its own right.[1] Leaving aside the contested nature of the non-randomised data on which this assertion is based, evidence shows that any such effect is mediated by adherence to protocols inherent in trials.[13] Although the trial effect may provide overall assurance that sponsoring trials is not harmful at the population level, it certainly cannot be used as an inducement, since, far from offering enhanced care to participants, clinicians are charged with the responsibility to guarantee that care will be unaffected should the offer of randomisation be declined.

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