Equipoise, consent and the ethics of randomised clinical trials

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A doctor has a duty to give his patient what he believes to be the best treatment. An ethical prerequisite of recommending her to enter a randomised clinical trial (RCT), in which his patient will be randomly allotted to one of two or more treatments, is, as Michael Baum in his chapter stresses, that he is ignorant about their relative efficacy and, hence, justifiably indifferent as to which she receives. Writers[1] who deny that a doctor's duty to his individual patient can be overriden by the need to advance science and so benefit future patients[2], commonly attack RCTs by asserting that rarely, even at the outset of an RCT, can a doctor be indifferent to the treatments being tested. Consequently recommending[3] his patient to enter an RCT will almost invariably contravene his duty to give her the treatment he believes to be the best.

Summary of the argument

My argument will be that this wholesale scepticism about the possibility of a doctor's indifference (due to ignorance) as to which treatment his patient receives, obscures the important distinction between situations in which patients are and those in which they are not prepared to make trade-offs between the advantages and disadvantages of particular treatments. Consider, for instance, a patient with breast cancer who does not discount the importance of prolongation of life when disfigurement is at stake. Though prior case histories may suggest that lumpectomy is as efficacious, in terms of survival, as mastectomy, the dubious evidential value of these histories means that a doctor really cannot, prior to an RCT exclude the possibility that mastectomy may finally be found to be the better treatment for her.

But, as I shall indicate, a doctor's very scepticism as to the validity of the prior 'evidence' now raises embarrassing questions, for *supporters* of RCTs, concerning the permissibility of depriving patients, who have been randomly allotted to lumpectomy, of a treatment, such as mastectomy, with its acknowledged track record concerning survival. The source of this dilemma, I shall suggest, is the traditional polarisation of cognitive states into either knowledge or mere belief or 'opinion' which underlies current notions of equipoise. I finally propose a new approach, utilising ideas from Bayesian statistics, that allows the postulation of a grading of evidence as to the comparative value, all things considered, of two treatments, which is neither too weak nor too strong to exclude using RCTs.

Should, however, the requirements for a permissible RCT be thus far met (perhaps by utilising the Bayesian method), it might still be objected that it is wrong for doctors to allow their patients to submit to medical procedures whose primary aim is to advance knowledge and help future patients rather than to benefit the individual. I ask therefore whether obtaining a patient's informed consent could, as some writers believe[4], absolve the doctor of this deliberate failure to put his patients' interests first, and suggest that an affirmative answer depends upon a still controversial interpretation of the doctor-

patient relationship. I consider (in the postscript) whether it is morally acceptable to use the Zelen method of pre-randomisation to minimise the requirement of informed consent for RCTs.

The charge of incompatibility

'The charge of incompatibility', as I shall term it, is broader than just the claim that a doctor may *sometimes* have to choose, during an RCT, whether to sacrifice his patient's interests to those of scientific progress as, for example, when a developing trend in the evidence, though not decisive statistically, nevertheless suggests that the treatment allotted to a patient may be harmful[5]. This dilemma, it is held, already confronts doctors at the outset of an RCT, and hence even before any trend might be apparent, since a doctor can never be genuinely indifferent as to which of the treatments being tested should be given to his patient. Fried suggests why this should be so in his pertinent question: 'Is it ever likely to be the case that in a complex medical situation the balance of harms and benefits discounted by their appropriate probabilities really does appear on the then available evidence to be in equipoise?'[6]

Schafer, developing Fried's point, suggests that frequently two treatments will only appear equivalent if the factors taken into account in assessing their comparative worth are restricted to gross measures, such as mortality and morbidity. Once, however, 'all the patient's circumstances, including his attitudes and value system are brought into the equation... the risks and benefits of the treatment alternatives will lose their equilibrium'.[7]

To illustrate their 'charge of incompatibility', critics of RCTs typically cite the following example. Suppose a doctor wishes to compare, as treatments for stage 1 breast cancer, mastectomy with lumpectomy. The doctor suspects that these treatments are of equal efficacy in terms of recurrence and survival, yet only one of them involves the removal of the whole breast and thus what many women would regard as serious disfigurement. To a patient randomly assigned to mastectomy, whom he knows fears disfigurement, he can promise no advantage in terms of survival compared with the women who receive the less aggressive therapy, mere removal of the lump. If the doctor *could* promise her longer survival, he could hardly morally justify allowing *other* patients to receive mere lumpectomy. But if he can promise her no advantage, how can he defend subjecting *her* to mastectomy, rather than patients who may care less about disfigurement or even wish for the removal of their 'offending' breast? Either quality of life is not to be taken into account in determining the better treatment (which seems unacceptable) or, if it is, we are faced with a doctor's apparently flagrant disregard of his patient's interests. As this is part of a deliberate attempt to gain knowledge for the benefit of the larger population of breast cancer sufferers, he may, with some justice, be described (to borrow a phrase from Baum's paper[8]) as using his patient merely as an instrument for research.

But *defenders of RCTs*[9] will argue that, though a doctor has a duty to give his patient that treatment he believes to be the better, there would be no point in instituting an RCT if he already knew which it was. If he does not know which treatment is the better, and is hence in a state of 'clinical equipoise', how, in this situation, could he be charged when entering his patient into an RCT, with violating his duty to give her the better treatment?

Schafer's and Fried's position depends upon treating what is undoubtedly true for a few as if it were true for all patients. Of course some patients value the (certain or possible) advantage that one treatment offers so highly that they are not prepared to risk being allotted the other treatment. Consider, for instance, a woman not prepared to undergo mastectomy even when she is told that

there is an 80% chance of surviving more than five years and chooses to have a lumpectomy although she knows that there is no assured survival rate. Assuming that a doctor should take into account his patient's preferences in deciding which is the better treatment for her, this woman's doctor can already tell, even before the comparative survival rates for mastectomy and lumpectomy are known, that lumpectomy is, all things considered, the better treatment for her. Consequently, it would be quite indefensible for him to recommend her entry into an RCT in which she runs the risk of being randomly allotted mastectomy. Again, a doctor could not justifiably recommend a woman who simply wants to be rid of her 'offending' breast to enter an RCT of mastectomy against lumpectomy. Since she is quite uninterested in the suggestion that perhaps lumpectomy may prove as effective for survival as mastectomy, her doctor can already confirm that mastectomy is the better treatment for her.

But patients may frequently be prepared to make trade-offs between the advantages and disadvantages of treatments. Their position will be this: 'I will not discount the importance of the high chance of surviving at least five years which mastectomy promises and which, if lumpectomy turns out to have an inferior survival rate, will mean a greater prolongation of my life. But neither will I discount the chance that lumpectomy will be found to have the same survival rate as mastectomy and so I could escape disfigurement.' A doctor will be unable, prior to the RCT, to tell which is the better treatment, all things considered, for these patients and it will hence be justifiable for him to recommend them to enter it.

Fried's and Schafer's charge would only be convincing for these patients if comparisons, made before an RCT, of the relative merits (adjusted by their appropriate probabilities) of, for example, mastectomy and lumpectomy, were based upon *unbiased* estimates of the survival rates of the two treatments. But they cannot be; 'clinical equipoise' is precisely a state of indifference as to which of two treatments should be chosen *taking into account* the serious bias of estimates based on uncontrolled case histories and self-selected samples. It is, moreover, the very rejection by doctors and researchers of prior case histories as possessing a value as 'scientific evidence', and their determination to treat even estimates of probabilities based upon these as mere 'guesswork', that leads to the advocacy of RCTs.

That randomised treatment cannot be tailored to the patient's needs, though true, now loses much of its force. For, so long as doctors and researchers cannot give unbiased estimates for the survival rates of mastectomy as against lumpectomy, there is simply no valid account of the margin between survival rates for the treatments against which to balance the certain disadvantage of disfigurement. Hence even a detailed inquiry (as advocated by Schafer) into the priorities a particular patient assigns to, for example, prolongation of life against disfigurement, cannot, except in the instances detailed, help her doctor determine the better treatment for her. Consequently, in recommending her to enter an RCT, he does not sacrifice her right[10] to that treatment. Provided only that she is prepared to make *some* trade-off between prolongation of life and disfigurement, his advice to her must be that, even taking into account the known disadvantages to her of disfigurement, mastectomy could still turn out to be, all things considered, the better treatment for her. The claim that there is frequently a best treatment for a patient, when taking into account quality of life, besides survival and recurrence (which the RCT may demonstrate to be equal), should not be confused with the claim that a doctor can already tell before an RCT which is that treatment.

But *critics of RCTs* can now take up a different method of attack. If doctors and researchers when conducting RCTs feel justified in allowing some of their patients to forgo the officially more reputable or 'standard' treatment, especially when survival is at stake, then they must surely already have, to use Bradford Hill's words 'some basis' (eg. the results of past case histories, etc.)[11] for believing that, for instance, mastectomy is no more efficacious in terms of survival than lumpectomy. More than this,

they must judge that they can *safely* omit the standard treatment. Indeed Bradford Hill remarks upon 'the impossibility of withholding, even temporarily, any treatment for a disease in which life and death is seriously at stake'. A measure, then, of just how confident doctors and researchers are, on the basis of informal evidence, that two treatments, such as mastectomy and lumpectomy, are equivalent in terms of survival is their readiness to run an RCT.

But if a doctor confidently expects women to survive just as long after either treatment, Fried's charge arises once again. For the doctor is then confronted with an uncomfortable choice: either to disregard the importance of quality of life, since this would tip the balance in favour of lumpectomy as the better treatment for those women who fear disfigurement, or, admitting the importance of quality of life, to allow these patients to be possibly randomised to the worse treatment for them, viz. mastectomy. In these latter circumstances, as we have seen, it would hardly be ethical for a doctor to recommend that these women enter the trial, unless it were also argued that patients' interests can sometimes be overriden in the interests of science and humanity.

Clinical equipoise: old and new interpretations

The real dilemma facing doctors and researchers wanting to run an RCT is that the very reasons in its favour also militate against it. There is evidence, tentative and biased, of the equal performance of mastectomy and lumpectomy in terms of survival which prompts doctors to run an RCT. But to justify allowing some women, who fear disfigurement, to be randomly allotted to mastectomy, when the prior evidence suggests it carries no advantage as regards survival over lumpectomy, the *unreliability* of this evidence has to be stressed. But if the evidence *is* unreliable how can doctors justify depriving those women who are randomly allotted to lumpectomy, or mastectomy, given its established record?

No illumination is shed on this problem, but rather it is further compounded by those writers who state that for RCTs to be permissible the doctor must believe that 'there is nothing to choose between the treatments'[12]. For this rendering of the notion of clinical equipoise is so loose as, ludicrously, to make it consistent with doctors having *proof* of the equal performance in terms of survival rates of two treatments which either have no, or equivalently disadvantageous, side-effects. The only plausible remaining interpretation of the statement is as a disclaimer of any knowledge as to the comparative efficacy of the treatments to be tested, and this has the difficulties we have already catalogued.

Some writers[13], borrowing the language of contemporary statistical methods to capture the notion of clinical equipoise, assert that the experimenter must be able 'to state an honest null hypothesis'. But this is just as ambiguous as previous attempts to render the idea of 'clinical equipoise'. For sometimes stating an honest null hypothesis is taken to exclude any belief at all about the comparative efficacy of the treatments being tested[14]. At other times, the null hypothesis is taken as consisting in a judgement that certain gross measures of outcome are equal, for example (in the comparison of mastectomy and lumpectomy), that five years after the initiating of either treatment, the probability that the patient will be alive is the same[15].

Again, we are pushed in one of two directions. To accept the latter interpretation may seem to countenance, prior to the trial, a kind of confidence concerning the comparable performance of the two treatments that is ethically incompatible with running the trial. To reject it in favour of the former interpretation is, as we saw, with other renderings of the notion of clinical equipoise, to invite the charge that we have too categorically dismissed the value of informal evidence, amassed at the outset

of the trial and part of its *raison d'être*. But can we not avoid this kind of polarisation by postulating a quality of evidence which is neither too weak nor too strong to exclude a trial?

But all the versions of the notion of clinical equipoise that we have so far considered either embody, or are formulated against the background of, the traditional philosophical division between knowledge and proof, on the one hand, and opinion and belief, on the other. This stark division naturally cannot encompass the idea of subtle shifts and gradations in the strength of our evidence, and in the corresponding degrees of our confidence, before and after a trial. A few writers unenthusiastically attempt, from within this traditional cognitive framework, to give some slight weight to informal evidence, but many more appear to write it off. Gilbert[16] for instance, maintains that knowledge as to the comparative efficacy of treatments can only be achieved via randomised clinical trials, whilst statements made on the strength of uncontrolled studies must be regarded as 'ill-founded' and 'irrational'. They are nothing more than 'guesses' and hence 'likely to be wrong'. Indeed he cites experiments with highly intelligent students to confirm this view. Baum[17] too condemns 'much, if not most, of contemporary clinical practice [as] essentially based on forms of guesswork' and contrasts these with the scientific validation that can only be given by randomised clinical trials. 'The guessing' he says categorically 'has to stop'. Arthur Schafer[18] insists that since any treatment preference based on incomplete scientific knowledge 'falls well short of knowledge' it must be labelled 'bias or hunch'. V. Herbert[19] who admits that uncontrolled studies 'point in a direction', denies them the status of 'evidence' since only randomised clinical trials can 'tend to prove' or 'actually prove'. Even an authority of the stature of Bradford Hill, after uneasily allowing 'some' weight to the evidence without which he admits it would be impermissible to withhold an erstwhile standard treatment, nevertheless argues that prior to a trial, a doctor 'really has no knowledge at all as to whether one treatment will be better or worse, than the other'. Again he emphasises that the doctor's state is one of 'ignorance' in which he believes the choice of treatments is 'a matter of indifference'[20]. To support this extreme claim, however, Bradford Hill has finally to discount data which earlier he was prepared to describe as 'some' evidence, as no evidence at all.

None of these writers apparently realises that their categorical dismissal of the value of informal evidence raises insuperable problems for the formulation of a notion of clinical equipoise that could make trials, such as that comparing mastectomy and lumpectomy, morally permissible. For their remarks simply invite the sceptical question: how could a physician justify denying to any woman suffering breast cancer the erstwhile 'standard' treatment (mastectomy), on the basis of mere guesswork, hunch or bias and when he is willing to admit that his views are so far 'irrational' and 'unfounded'? They meet Fried's and Schafer's charge but only at an unacceptable cost.

I have already suggested that our only hope of resolving this problem lies in being able to postulate a quality of evidence, and a corresponding degree of confidence in the comparable efficacy of treatments, such as mastectomy and lumpectomy, which is neither too strong nor too weak to exclude a trial. The validity of this evidence would not be undermined by, but rather acknowledged in, the decision to run a trial, during which our prior degree of confidence would be readjusted and more tightly focused in the light of the new results. It is ironical, however, that amongst the statistical methods, the practise that writers have seized upon, and erected into an ethical requirement of RCTs, namely that of stating a null hypothesis, is particularly unsuited to this approach. In the first place, the null hypothesis functions as a sceptical disclaimer of any prior knowledge of whether or not the treatments are equally efficacious[21]. The thought behind its postulation is 'For all I know, there's no difference between the treatments - so let's test that'. But it is just this readiness to dismiss all prior evidence, and start, so to speak, *de novo*, that we are trying to avoid. Secondly, the point of stating a null hypothesis to the effect that the survival rates of two treatments, say mastectomy and

lumpectomy, are the same is to devise a decision procedure, viz. the randomised clinical trial, for accepting or rejecting it[22]. But because the null hypothesis, which requires the survival rates to be precisely equated, is once-and-for-all confirmed or disconfirmed, there is no scope for re-adjustments of prior degrees of confidence concerning the comparability of the treatments (even were these expressible within the method).

There is an alternative Bayesian approach[23] which, though advocated by many theoretical statisticians today, has not yet found favour with medical researchers. Bayesians would get doctors to express their prior belief in a range of survival rates, or hypotheses, in terms of their confidence in each of them. In other words, they would get them to attach a subjective probability to each hypothesis, based on their own experience and that of published reports. The aim of the RCT would then be to concentrate the prior degree of confidence over a narrower range of possible survival rates. The Bayesian approach, in contrast to the classical statement of a null hypothesis, followed by a decision procedure for its outright rejection or acceptance, allows us to express a degree of confidence in our beliefs which, rather than having to be entirely set aside at the outset of the trial, can serve as a basis, which the results of the RCT will improve. A continuity can thus be established between our prior and our subsequent confidence, only varying in its degree of strength. The prerequisite for running an RCT would now be not 'clinical equipoise', but rather that doctors and researchers possess a degree of confidence as to the equivalence of the respective survival rates for two treatments, e.g. mastectomy and lumpectomy, strong *enough* but not *too* strong to justify an RCT. It would be an interesting project[23] to work out in greater detail how quantified prior confidence in the efficacy in terms of survival of two treatments, such as mastectomy and lumpectomy, which would take into account the biased data, could be balanced against the certain side-effects.

The role of consent in RCTs

I want finally to set the 'charge of incompatibility' in a wider context and consider where its rejection leads. The approach outlined above allows us, as we have seen, to postulate a quality of evidence, as to the comparative efficacy of two treatments, which is neither too weak nor too strong to prohibit an RCT. This quality of evidence permits a *certain* degree of confidence in the merits of one treatment over the other, but it is insufficient to justify doctors in identifying the better treatment. For this increased degree of certainty they must await the outcome of the RCT. Thus, since prior to the RCT a doctor cannot identify the better treatment, he does not, by recommending his patient to enter an RCT, jeopardise his duty to her to give her this treatment. Hence the 'charge of incompatibility' fails. Of course, if trends arise during the RCT indicating that one of the treatments being tested is better than the other, there will be a corresponding shift in the degree of confidence of doctors and researchers in the comparative merits of the two treatments which will preclude the continuation of the RCT.

Consider now a doctor who assesses the comparative merits of two treatments and concludes that, given the present state of his knowledge, he cannot say which is better. If either treatment had a disadvantage which the other lacked, and which the doctor were to deem relevant to his decision as to which was the better treatment, then, by hypothesis, he would already have taken it into account in assessing the comparative worth of the two treatments. May we not conclude then that it is permissible for him to recommend his patient to enter an RCT comparing the treatments? But is it right for a doctor to allow his patient to submit to a medical procedure whose object is primarily to benefit others, even when her chance of getting the better treatment is not jeopardised?

The answer depends upon our precise understanding of the duty which a doctor owes to his patient. Suppose this is a duty simply to give his patient what he believes to be the better treatment or, at least, not to put her at risk of receiving what he believes to be the worse treatment. A doctor, as we have seen, may fulfil this duty whilst recommending his patient to enter an RCT, although its primary aim is to benefit future patients rather than her individually.

But it is dangerous (for reasons I discuss in the postscript) to circumscribe the doctor's duty toward his patient in this way. If, however, we add that a doctor is also forbidden from doing to his patient, or allowing her to undergo, anything which is not primarily aimed at benefiting her, there are just two possibilities: either RCTs even when a doctor genuinely does not know which is the better treatment for his patient, are impermissible, or obtaining a patient's informed consent to participation *makes* them permissible.

To claim that informed consent can make an otherwise impermissible RCT permissible is to give consent a role which goes beyond that which it plays in therapy. The patient's informed consent to a treatment is required to ensure that her doctor has neither subjected her to this treatment against her will nor manipulated her choice of treatment by concealing from her information about alternative treatments. But with RCTs there is yet a further danger. A patient could enter an RCT without realising that she will be subjected to medical procedures which are primarily aimed at benefiting future patients rather than herself. Her doctor might thus take advantage of her good faith that he will always put her interests first. Hence her informed consent to participate in an RCT is imperative.

But can a person, merely by giving consent, make another person's failure to fulfil his duty toward her any less wrong? Kantians show how autonomous persons can do this by waiving or alienating their rights. In their view, we are all, and not just doctors, morally prohibited from using people as *'mere* means' to our ends. Nevertheless an *autonomous* agent can *waive his right* not to be used by others for their ends. He will typically do so when he approves and wants to further these ends himself. Consequently, by consenting to being used by them for ends with which he either partly or wholly identifies, he absolves them of committing a wrong against him. Kantians would describe him as being used as a means but not, even should he suffer harm as a consequence, as a *'mere* means', to their ends[24]. Consider, for instance, a patient who consents, despite serious disadvantage to herself, to participate in an RCT because she wishes to do whatever she can to advance knowledge and so benefit future patients. She chooses to waive her right that her doctor put her interests first and thus absolves him of the wrong of failing to comply with his duty toward her.

But, it might be objected, patients are in no position to *waive* their rights. Indeed, on the traditional paternalistic conception of the doctor—patient relationship, the doctor's duty toward his patient does not arise out of a right on the part of his patient at all. In this respect it might be likened to the duties we owe animals or children or other persons who, because they lack autonomy, are often thought not to possess rights. Of course, if possessing rights were merely a matter of being owed other people's help or protection even persons of deficient autonomy (as patients are here regarded) could possess rights. But these would not be the kind of rights that the possessor could waive by an exercise of his autonomy. Many writers,[25] however, argue that a person cannot properly be described as possessing rights if he is not considered responsible enough to be able to choose to waive them. Hence they stipulate that we should speak only of the *duties* which other people owe to such a person. Now, just as it does not make sense to suppose that such a person (a child would be a typical example) could release us from these duties, so it would seem inconceivable that the patient, on the traditional conception of the doctor-patient relationship, could so release her doctor.

The claim that a patient may, by consenting to participate in an RCT, absolve her doctor for any wrong he thus commits against her awaits, for its confirmation, the development of a new model on which to base the doctor-patient relationship. The new model would extend what is sometimes called a 'choice conception of rights' to the doctor-patient relationship. The patient's autonomy would then be regarded as capable of overriding considerations of beneficence, and hence it would be acknowledged that the doctor-patient relationship is one between equals.

The Zelen method of pre-randomisation; a postscript

Many doctors[26] are acutely aware of the conflict between their duty toward their individual patients and that which they owe to the larger population of future sufferers. To minimise this conflict, doctors and researchers who want to test a 'standard' treatment against, say, a combination of the 'standard' treatment and a new one, may use Zelen's[27] single pre-randomised design (as opposed to a symmetrical or double pre-randomised design[28]). This involves randomising patients *before* rather than *after* consent. Consent is then sought from those patients randomised to the 'standard plus' treatment: if they should refuse consent they are assigned to the 'standard' treatment. But doctors argue that it is unnecessary to seek the consent of patients who have been allotted to the 'standard' treatment since they will receive the 'recognised best' (i.e. the 'standard') treatment anyway. Doctors fear that, were these patients to learn that there existed an alternative treatment, which promises all the benefits of the 'standard' treatment combined with possible new benefits, they might refuse to take part in the RCT and, demanding the 'standard plus' treatment, prejudice the success of the trial.

There are several difficulties with Zelen's method of pre-randomisation as an ethically acceptable way of minimising the need for consent. First, if, as we have assumed, a doctor should generally take into account his patient's preferences in deciding which is the better treatment for her, the 'standard' treatment will not necessarily be the better treatment. For, as in the case under discussion, a patient may prefer an alternative treatment to the 'standard' treatment.

There are, of course, rare instances where having her preferences met would not be in a patient's best interests. Suppose, for instance, that a patient objects to being temporarily hospitalised though this may not only save her life but return her to full health. Or suppose that the patient herself acknowledges that what she wants is not what is in her best interest. So, she might tell her doctor that she wants a less aggressive treatment because fear of the more aggressive procedure haunts her. She is, however, quite willing to admit that the latter could ultimately be of longer benefit and hence that it is in her best interests to submit to it. But the patient's preference for the 'standard plus' treatment can hardly, in the example we are discussing, be dismissed as wayward or irrational since her doctor is prepared to submit half of his patients to it.

Second, it would seem wrong for a doctor, even when he thinks he knows which is the best treatment for his patient, to suppress from her information about alternative treatments. Doctors defend their action by arguing that if they were to tell a seriously ill patient about an alternative treatment which, though less aggressive than the treatment which they recommend, was in their opinion ineffective, she might put her life at risk by choosing it. They ask where they are to draw the line if they are obliged to inform patients even of such treatments? Should they, for instance, also tell their patients about quack 'cures' and 'natural' remedies, such as are offered by homoeopathists? Whilst these arguments have some force we cannot, I believe, condone a doctor's manipulation of an autonomous patient's choice by concealing information from her. But doctors can hardly disregard a patient's preference for

the 'standard plus' treatment on the grounds that it is unsafe since, as we have observed, they are willing to submit half their patients to it.

Finally, doctors withhold information about alternative treatments in the course of ordinary therapy with the sole purpose of benefitting their individual patient and so are merely paternalistic. But doctors using the Zelen method of pre-randomisation conceal from their patients the existence of an alternative treatment to the 'standard' treatment largely to ensure satisfactory recruitment to an RCT which they hope may advance knowledge and so help future patients. For them, the requirement of informed consent is, as one doctor has frankly put it, 'an unfortunate obstacle to scientific progress'[29]. But in thus manipulating the patient's choice, not in her own but in other patients' interests (which could conflict with her interests), they use their patient, as Kantians would argue, as a 'mere means' to their ends. Yet supporters of the Zelen method of pre-randomisation do not see how this can be wrong since, they claim, they are giving their patient what they believe to be the best treatment. We can only conclude that their account of the doctor's duty is dangerously deficient. A doctor has, as they rightly point out, a duty to give his patient what he believes to be the better treatment or at least not to put her at risk of receiving what he already knows is the worse treatment. But he must also refrain from doing anything to his patient which is not for her benefit, unless he first obtains her informed consent. This, however, entails a role for informed consent in making RCTs permissible which requires the abandonment of the paternalistic conception of the doctor—patient relationship.

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Notes and references

[1] Arthur Schafer, 'The Ethics of the Randomized Clinical Trial', *The New England Journal of Medicine*, 307 (1982) p. 720; C. Fried 'Medical Experimentation: Personal Integrity and Social Policy', in A. G. Bearn, D. A. K. Black and H. H. Hiatt (eds), *Clinical Studies*, Vol. 5 (New York: Elsevier, 1974); I Kennedy 'Consent and Randomized Controlled Trials', in his *Treat Me Right* (Oxford: Clarendon Press, 1988) pp. 219-20, 222.

[2] Michael Baum, in 'The Ethics of Clinical Research' (the preceding chapter of this volume) argues that it is not only permissible but obligatory to enter patients into RCTs, since any possible disadvantage to an individual patient is quite outweighed by the advantage for future patients of obtaining knowledge that will combat disease. Indeed for him it is the 'scientific necessity' of RCTs, as the only means of obtaining the requisite knowledge, which makes them morally obligatory. He maintains, however, that, except where there are therapeutic reasons against it, not seeking the patient's consent is morally wrong, since it violates her autonomy.

[3] I assume that it would, in these circumstances, be wrong even to *recommend* patients to enter an RCT since doctors have a duty to offer the best advice to patients. It may be objected that patients can make up their own minds despite such a recommendation. But as Schafer, Kennedy and others point out, sick patients tend to defer submissively to their doctor's advice and hence may well be incapable of giving a proper informed consent.

[4] Kennedy, 'Consent', p. 220.

[5] Ibid., p. 219.

[6] Fried, 'Medical Experimentation'.

[7] Schafer 'The Ethics', p, 720.

[8] Baum, 'The Ethics'.

[9] Sir Austin Bradford Hill is perhaps the most famous, see his *Principles of Medical Statistics*, (London: *The Lancet*, 1971) pp. 245—7.

[10] I discuss the appropriateness of using the notion of rights in this context later in the chapter.

[11] Hill, *Principles*, pp. 245-7.
[12] A form of expression frequently used by researchers, see Schafer, 'The Ethics', p. 722.
[13] R. J. Levine, 'Ethical Issues in Clinical Trials', in V. Mike and K. Stanley (eds). *Statistics in Medical Research* (New York: John Wiley, 1982) p. 164-5.
[14] See D. Vere, 'Problems in Controlled Trials,' *Journal of Medical Ethics*, vol. 9 (1983) pp. 85—9, cited by Peter Byrne in his helpful article 'Medical Research and the Human Subject', in Callahan and G. R. Dunstan (eds), *Biomedical Ethics: An Anglo-American Dialogue* (New York; New York Academy of Sciences, 1988) p. 151.
[15] Levine 'Ethical Issues', p. 165, and again in R. J. Levine, 'Protection of Human Subjects of Biomedical Research in the United States' in Callahan and Dunstan (eds), *Biomedical Ethics*, p. 137. Here again Levine misleadingly associates the null hypothesis with 'the judgement that two treatments are potentially medically equivalent in terms of such gross outcome measures as life expectancy and probability of recurrence of cancer'.
[16] J. P. Gilbert, 'Statistics and Ethics in Surgery and Anesthesia' in 'A Symposium on Medical Research: Statistics and Ethics', *Science*, vol. 198 (1977) p. 687.
[17] Baum, 'The Ethics'.
[18] Schafer 'The Ethics', p. 723.
[19] V. Herbert 'Acquiring New Information While Retaining Old Ethics', *Science*, vol. 198 (1977).
[20] Hill, *Principles*, pp. 245-7.
[21] See W. Silverman, *Human Experimentation*, (Oxford: Oxford Medical Publications, 1985) p. 116.
[22] J. B. Kadane, 'Progress Toward a More Ethical Method for Clinical Trials', *Journal of Medicine and Philosophy*, vol. 11 (1986), p. 385-405.
[23] A helpful, not too mathematical, account of the Bayesian principles is: L. D. Phillips, *Bayesian Statistics for Social Scientists* (London: Nelson, 1973).
[24] For an analysis of Kant's notion of 'using someone merely as a means to an end', see my 'Abortion, Embryo Research and Foetal Transplantation: Their Moral Interrelationships', in Peter Byrne (ed.), *Medicine, Medical Ethics and the Value of Life*, (Chichester, John Wiley, 1990) pp. 51-8.
[25] For a helpful account of the two different conceptions of rights, see L. W. Sumner, *The Moral Foundation of Rights* (Oxford: Clarendon Press, 1989) pp. 93-111.
[26] J. Tobias, 'Informed Consent and Controlled Trials' *Lancet*, vol. ii (1988) p. 1194; see also Baum, 'The Ethics'.
[27] M. Zelen, 'A New Design for Randomised Clinical Trials', *New England Journal of Medicine*, vol. 300 (1979) pp. 1242-5. Helpful articles on the Zelen method are D. Anbar, 'The Relative Efficiency of a Zelen's Prerandomized Design for Clinical Trials', vol. 39 (1983) pp. 711-8 and D. Marquis 'An Argument that All Prerandomised Clinical Trials Are Unethical', *Journal of Medicine and Philosophy*, vol. 11 (1986) pp. 367-85.
[28] Here patients who are pre-randomised to the standard treatment are also given the option of receiving the alternative treatment.
[29] Tobias, 'Informed Consent'.