Equipoise and the ethics of randomization

Richard J Lilford MRCOG MRCP MFPHM[1] Jennifer Jackson MA[2]

J R Soc Med 1995;88:552–559

Keywords: *equipoise; ethics; decision analysis; clinical trials; randomized clinical trials*

INTRODUCTION

It is widely accepted that randomized controlled clinical trials yield the most reliable evidence about the effects of clinical care[1]. In this article we discuss the ethical importance of 'equipoise'—the condition which applies when there is no preference between the treatment options to be compared. We ask whether equipoise is an essential prerequisite for an ethical trial: are trials ethical only if there is no preference between treatments? If so, who must have no preference—clinical experts, individual clinicians and/or the potential participants (patients)? Does it make any difference whether there is open access to contending treatments or whether one (or more) of them are 'new' and less available. Lastly, if equipoise is an essential prerequisite for an ethical trial, what are the implications for clinical science? Clinical trials may examine a number of competing treatments simultaneously but, for ease of description, we consider the case of two treatments; A and B.

INDIVIDUAL AND SOCIAL OBLIGATIONS

Clinicians and ethics committees are concerned with two sorts of obligations: the obligation to safeguard the rights of individual trial participants and the obligation to society to facilitate research aimed at improving medical treatment—let us call these 'individual obligations' and 'social obligations'.

Does randomization, as such, create a tension between these two obligations? The individual obligation requires that each patient is offered one or more treatments deemed to be appropriate for that particular person. Under randomization, treatment is assigned according to the imperatives of the experimental design.

However, since the whole point of holding a trial is to find out which treatment is more appropriate, participants, even if they were acting from a purely egoistic point of view, would have no reason to object to randomization as such. Being randomized does not disadvantage them (for reasons given below it may even advantage them) and does advantage society. Ethics committees and clinical researchers then should have no difficulty reconciling individual and social obligations on account of randomization: any trial worth carrying out is a reasonable bet for individual participants[2].

Of course, matters are not so simple. The underlying simplistic assumption here is that if we do not yet know which treatment is better we are not defaulting on our obligation to give the most appropriate treatment by assigning treatment at random. Where we do not know which treatment is better we may all the same, in advance of proposed trials, have our (more or less rational) preferences. Believing and disbelieving come in degrees: the results of previous trials (perhaps too small to place the issue beyond reasonable doubt), observational studies, the history of medicine's past mistakes and the biological plausibility of a treatment all legitimately influence the degree of our prior belief[3].

EQUIPOISE

Equipoise is the point where there is no preference between treatments, i.e. it is thought equally likely that treatment A or B will turn out to be superior[4]. At this point we may be said to be 'agnostic' or 'resting' on the fulcrum of a decision: we would take odds of 1:1 in a bet. Equipoise is different from simply not 'knowing' or being 'uncertain', because it implies that we have no (rational) preference whatever. We could have a mild preference for treatment A and still not 'know' which treatment was best: we would be uncertain but not in equipoise.

Individual equipoise (referred to by Freedman as theoretical equipoise[5]) applies to individual clinicians whilst collective equipoise (also known as clinical equipoise) refers to the profession as a whole (or at least those sections of the profession who are perceived to be 'expert' in the subject—we return later to the question of who is 'expert'). Individual equipoise demands an opinion from the individual that the evidence is equally split, i.e. it is perceived to favour neither treatment A nor B or to favour them equally.

IS COLLECTIVE EQUIPOISE NECESSARY?

It could be argued that an adequate procedure for obtaining consent would suffice to screen out trials which are unethical in principle. Who, after all, would agree to participate if,

[1]Chairman, Institute of Epidemiology and Health Services Research, [2]Senior Lecturer, Department of Philosophy, University of Leeds, 34 Hyde Terrace, Leeds LS2 9LN, England, UK

Correspondence to: Professor R J Lilford

having been given all relevant information, participation appeared contrary to their own best interests?

All the same, we do need to separate the questions of principle from the procedural questions. No matter how sophisticated the procedural rules are that we adopt, they do not ensure that consent is genuine. The getting of genuine (informed and voluntary) consent is notoriously tricky[6–9]. Hence we cannot *rely* entirely on procedural safeguards (important as such safeguards are—a point to which we shall return). The very existence of ethics committees engenders a certain level of dependency, because a potential participant may assume that the trial has been seen as reasonable by a separate, informed and authoritative panel charged with safeguarding the interests of participants. Furthermore, some trials address questions, where it is impossible or impractical to get consent.

Thus, members of ethics committees should proceed on the basis that the question to be investigated has not already been answered. In some cases, the evidence may be compelling and the 'experts' (however defined) may all be in agreement as to which treatment is best. Under these circumstances the trial would be unethical. Alternatively, the data may be confused and contradictory, and the 'experts' divided equally amongst themselves (less plausibly the experts might be all individually equipoised). Under these circumstances the ethics committee could find the trial ethically acceptable. Assuming that an ethics committee perceives the experts as all well qualified to comment, then patients would seem to have nothing to gain or lose from trial entry. In reality, however, most cases coming before a committee probably lie somewhere between these two extremes—collective equipoise would be incomplete in such instances.

Johnson and colleagues[10] carried out a survey among members of the public and found that, while most accepted the practice of randomization when expert opinion was evenly split, less than 3% considered trials to be acceptable if opinion was split 80:20. (Greater deviations from an equal split in opinion were tolerated when the treatment could be repeated, i.e. when it was not a putative life saving intervention and, therefore, where participants in the 'inferior' arm of the study would be only temporarily disadvantaged.)

Ethics committees, it would seem, do not need to satisfy themselves that collective equipoise is exactly evenly balanced. This is fortunate because there is a practical problem over how ethics committees can assess collective equipoise. This might be: informal information (e.g., opinions of local clinicians); semi formal (e.g., evidence of different practice by doctor/locality/ or different opinions in the literature); or formal by specific measurement of expert belief[11–12]. Just whose views are worthy of respect (and thus who may be considered 'expert') may be a matter of some controversy. And even supposing that the 'experts' can be identified, it cannot be assumed that their strength of belief will always correspond to the strength of the evidence. Many trials (e.g., those of treatments for AIDS) are the subject of public attention[13] and ethics committees may wish to include patients' representatives among the 'experts'. The ethics committee may decide to examine existing evidence itself—in that case it becomes the relevant body of 'experts' who need to be in some agreement—to have reasonable collective equipoise. It is not straightforward to guage the extent of collective equipoise but it remains the underlying principle which makes a trial ethical from the perspective of an ethics committee. Of course, that does not make it ethical—individual professionals and potential participants must also judge it to be so—and this takes us to our main argument.

EQUIPOISE AND THE CLINICIAN : PATIENT RELATIONSHIP

Once a trial has been approved by an ethics committee, it is the individual clinician who must make or withhold the offer of entry in a trial and who must decide what to tell the patient in obtaining consent. Clinicians are in a strong position over inviting people to participate in trials where there is collective equipoise and when they themselves are equipoised (as in the trial of cervical cerclage to prevent recurrent miscarriage)[14]. The entry criterion for this trial was that the individual doctor could not decide, in a particular case, whether cerclage would prevent or promote fetal loss.

What though if, as is often the case, collective equipoise applies but the clinician is not in a state of individual equipoise? If such clinicians are to follow the familiar principle, 'do as you would be done by' (hence disclosing their lack of equipoise or not offering trial entry in these circumstances), then we might have to accept low recruitment for many important trials needed for the advance of science (and hence for the benefit of mankind—a point to which we return later). For example, a small but well conducted trial, suggesting that A was more effective than B, with a P value of 0.2, might lead a previously equipoised clinician to conclude that it was more likely than not that A was more effective than B. Could this clinician then act as though having no opinion about the relative effectiveness of these two therapies?

A crucial contribution to this debate has come from Freedman who appears to offer a way out[4]. Freedman argues that doctors are not bound by the principle, 'do as you would be done by'. Rather, they are bound by the consensus of expert opinion, by collective equipoise. In justifying this opinion, Freedman points out that the criteria for entry into a specialty and for censure in negligence cases are based on

adherence to collective norms. Thus, Freedman argues, offering trial entry is ethically acceptable provided that the profession as a whole (or at least 'domain experts') are divided on the issue, i.e. provided there is no collective agreement as to which treatment is better. If the profession as a whole is equipoised between A and B, then, according to Freedman, a clinician who prefers A can still ethically offer a patient entry in the trial.

We are concerned that this argument may not give sufficient weight to the requirement not to violate trust. It could be argued that ignoring a lack of personal equipoise violates the trust between patient and doctor and thus one of medicine's core values. James Spence (1960)[15] wrote that:

> the essential unit of medical practice is the occasion when, in the intimacy of the consulting room, a person who is ill, or believes himself to be ill, seeks the advice of a doctor whom he trusts. This is a consultation, and all else in medicine derives from it.

Confidence is thus at the heart of the clinician/patient relationship, which must be 'a real human relationship based on love, caring and sharing'. At issue here is whether the clinician is justified in behaving as though having no preference, when this is not the case. Most patients might expect their clinician either to withhold the offer of trial entry or declare any preference and would feel that Spence's principle had been overturned if this was not done. *If* this is so and *if* the importance of maintaining trust between clinician and patient is paramount, *then* the presence or absence of individual equipoise should affect how a clinician behaves.

We are not the first people to point out the conflict between private and public duties which a lack of equipoise can unmask. Freedman, as we mentioned, suggested a way out of this potential difficulty by distinguishing between collective and personal equipoise and claiming the primacy of the former. Others have suggested randomization in unequal ratios[16], but this can only maximize group, not individual, expected utility. It does not help an individual patient to know that her chance of drawing the less preferred treatment is, say, one in four, rather than one in two. Yet others have suggested randomizing patients to clinicians whose lack of equipoise lies in different directions[17], but this might not go down well with many patients especially if a relationship has already been formed with a participating clinician.

OBLIGATIONS OF DOCTORS/EXPERTS TO INFORM THEIR BELIEFS

The above argument does not entitle clinicians to deviate from equipoise for frivolous reasons. A sincere attempt to understand the issue must be made by clinicians who have a personal preference in the face of collective equipoise. Doctors and patients' representatives need to be advised of history's lessons and they have an obligation to keep as up to date as possible, to be sceptical of unsubstantiated claims and reluctant to form a view in the absence of in-depth knowledge. The ethically difficult cases are those where the clinician is party to evidence which is contradictory and/or weaker than that associated with conventional levels of statistical significance. It is in these cases that different people, equally well informed, intelligent and sincere, will form different opinions about the *likely* effects of treatment. This article considers how we should behave when this happens.

EXCEPTIONS TO THE REQUIREMENT FOR INDIVIDUAL EQUIPOISE

Are there circumstances under which it is acceptable (desirable) for clinicians to ignore lack of personal equipoise? We argue that the importance of personal equipoise is greatly diminished under conditions where access to the preferred treatment is limited, irrespective of whether or not a trial is taking place.

First, randomization against a lack of personal equipoise is permissible, indeed desirable, when access to treatment is in any case limited as a result of inadequate resources. Here, randomization also serves as an egalitarian method to allocate scarce resources. Lockwood and Anscombe[3] cite the example of doctors in India, who were not able to obtain sufficient anti-pseudomonas vaccine for burn patients, and allocated this treatment on the basis of randomization.

Secondly, open access to the preferred treatment may be limited, not because of financial constraints, but because a central authority (e.g., third party payer or health department), has decided that the treatment requires better evaluation in the public interest. This applies particularly to new technology, where the individual clinician's belief may not be widely shared (i.e. there is collective equipoise) or where there is doubt as to whether putative benefits are sufficient to outweigh the costs of the new treatment. A good example of the latter, is the randomized trial of extra-corporeal membrane oxygenation, currently taking place in the UK. Thus, it is possible for a third party payer to be acting in an ethically acceptable way in restricting access to new treatments (to people in trials), while an individual clinician might be acting in an ethically acceptable way in recruiting patients to the same new treatment despite having a personal preference for the new therapy. This is because the third party payer is responsible to people in general while the clinician is responsible to an individual whose best hope, in these circumstances of restricted access, can be realized by trial entry. We also make the observation that, as a general rule, an ethical obligation to maximize perceived utility for individuals, if it applies, is likely to restrict trials which are desirable for society as a whole[18]. This, therefore,

is an argument for restricting access to new technology to people in trials. Put another way, it may be inappropriate to ask clinicians and their patients to be the principal gatekeepers of developments in practice—a point to which we shall return.

THE PSYCHOLOGICAL EFFECTS OF TRIAL ENTRY

Participants in trials may find the experience of randomization disturbing[19–20]. On the other hand, they may be privileged patients. So far we have simply assumed that participants in trials who turn out to have been in the inferior arm of treatment have been disadvantaged. To be sure they are worse off than those who receive the superior treatment, but are they worse off than if they had not participated? While patients who decline to participate in trials are not deliberately neglected, trial protocol may necessitate close and extensive monitoring of participants so that, in effect, participants might regard themselves as beneficiaries[21]. If that is true, it may be that even those participants in trials who turn out to have ended up in the inferior arm of the trial, have not overall been disadvantaged. This may incline an outside observer to favour trials in general. It may convince an ethics committee to sanction a trial despite some misgivings, say about potential psychological risks or the degree of departure from collective equipoise. However, it hardly excuses an individual clinician in ignoring equipoise. In so far as patients may do better overall in clinical trials, this must be because of some treatment variable—perhaps rigour in following protocols or the psychological boost from extra attention. At the point where the offer of trial entry is made, the intention is to compare two treatments, not to give better overall care. A clinician cannot argue that equipoise was ignored because he or she would compensate by giving better care. Thus, the argument that participants may be beneficiaries cannot be used to gainsay the importance of equipoise. Put another way, a patient who was offered entry in a clinical trial, and who then learned that her doctor had failed to disclose a personal preference, would not feel any less aggrieved on hearing that this was because the doctor anticipated giving a higher standard of care on account of his/her participation in the trial.

EQUIPOISE AND PATIENT VALUES: THE TRADE-OFF BETWEEN BENEFIT AND SIDE EFFECTS

Thus far in the discussion we have rather naively assumed that treatments are simply better or worse, e.g., an increase or decrease in the risk of death at no differential cost—the situation referred to in decision analysis as one of probabilistic dominance. However, we must consider the more usual case where treatments are not simply better or worse. Most treatments have more than one effect and these effects may move in opposite directions. Here, perceptions of patients must come into the picture since the best treatment is not defined simply by probabilities of outcomes, but also by how these outcomes are valued[22]. Thus, where a treatment has well known side effects, the point of equipoise is not 'no effect' but an effect big enough to compensate for its perceived disadvantage: the point defined by decision analysis as that where the expected utilities of both treatment options are the same[23–25]. We call uncertainty around the point of no treatment effect 'absolute' equipoise, and uncertainty around the point where the patient has no preference 'effective' equipoise (Figure 1). (This could be called the patient's equipoise, but it is in reality the point where the patient's trade-off value corresponds with the clinician's expectation of the most likely treatment effect.) To give an example, let us consider trials comparing conservative with radical surgery for early breast cancer. Clearly, the second of these treatments has a known side-effect—namely, greater mutilation. Thus, the point of 'effective' equipoise is not 'no difference' between treatments, but a difference which compensates, but only just compensates, for the mutilation of extensive surgery. Thus, if a woman would sacrifice 2% of her chance of surviving for 5 years in order to avoid mutilation, then her point of effective equipoise is a 2% gain in 5 year survival. (This crude trade-off is given for pedagogic purposes. A more refined method would consider the different probabilities of death and disability in each year following treatment, along with the probabilities of moving from one

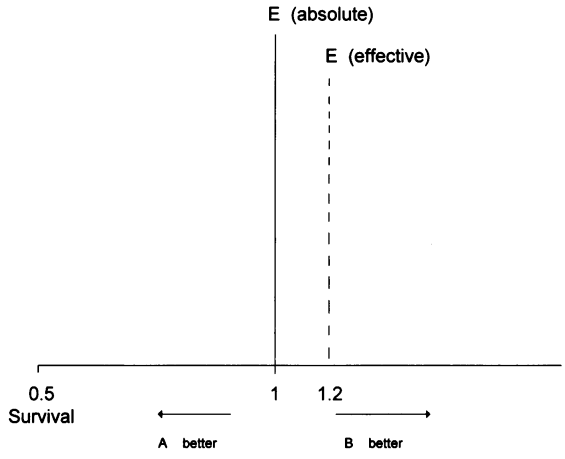

Figure 1 **Effective equipoise occurs when the most likely results (of a proposed trial) are thought to be an improvement sufficient, but only just sufficient, to compensate for the disadvantage of the treatment with the greatest 'costs'. Those 'costs' are side-effects when viewed from the point of view of the individual patient, or the combination of those side-effects and monetary costs when viewed from the perspective of society. In this example treatment B has greater 'costs' than treatment A, such that an improvement in mortality of about 20% would be sufficient to compensate for them. Put another way, an improvement in mortality of less than 20% may not be sufficient to offset the 'costs'**

state to another—Markov chain analysis.) This has implications for study design, since, if this were a typical response, the study should be sufficiently large to measure a treatment effect of this magnitude. The point of effective equipoise would be 2% if:

1 this was the trade-off which a patient would be prepared to make, and
2 this was also the treatment effect which her doctor thought most likely in advance of the trial

Standard (so called frequentist) analysis of clinical trials requires a starting hypothesis, typically that there is no difference in outcome across treatments—the 'null hypothesis'. According to our analysis, prior belief in a null hypothesis (absolute equipoise) is an unsound basis for clinical trials where there is a perceived trade-off between putative benefits and side-effects. Here, if the trial were ethically carried out, the starting hypothesis should be an effect corresponding to mean effective equipoise.

Thus, in circumstances of a trade-off (where one of the treatments has a perceived side-effect) the point of individual 'effective' equipoise is based not only on the clinician's beliefs about likely treatment effects, but also the patient's preferences.

The 'preference' trial takes these considerations seriously—here a potential participant can choose treatment A, treatment B or randomization. The latter is appropriate if the patient's values and the doctor's best guess of likely treatment effect coincide. In some cases a patient, perhaps a specialist in the subject concerned, may not wish to abrogate the judgement of the most likely treatment effect to her care giver and may form her own opinion on this point. However, this does not change the essential point that she is not likely to accept randomization unless the probability estimate and trade-off value coincide. It has been suggested that effective equipoise is less likely to occur when trade-offs are forced by comparisons of treatments with dissimilar side effects, i.e. where effective rather than absolute equipoise is required[26]. There are many examples of trials carried out in the face of large trade-offs and these frequently involve surgical procedures. Examples include, medical versus surgical therapy for menorrhagia, lithotripter versus surgery for ureteric stones, chorion villus sampling versus amniocentesis for prenatal diagnosis and Caesarean childbirth versus trial of vaginal delivery for the mature breech presentation. In all of these cases it must be the minority of patients who, in the face of all current information, will be in effective equipoise and hence who will agree to be randomized—in all of these cases a high recruitment rate must call into question the comprehensiveness of counselling. New treatments have potential unknown side-effects, the probability of which will be perceived to vary according to the nature of the treatment. This probability is one of the negative effects that a patient must consider in deciding whether or not she is in effective equipoise. Of course, the perceptions of good or harm may change with time, with consequent changes in recruitment[27]—however, sincere decisions can only be made on the basis of information available in prospect.

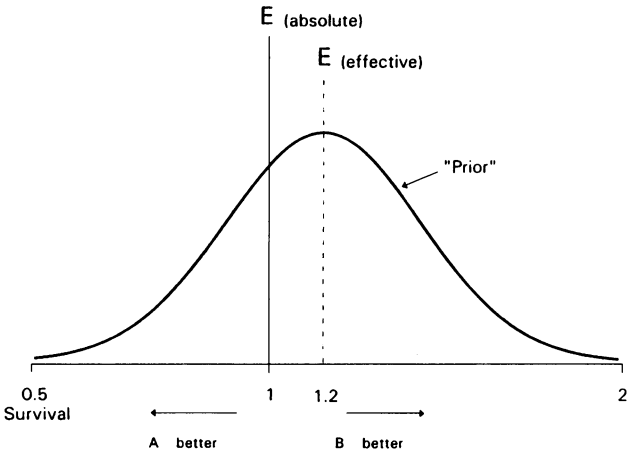

Figure 2 **The line marked 'prior' is the probability distribution of the expected results of a proposed trial showing that, the greater the deviation from the expected result (20% improvement) the less likely it is to happen. This could be based on the opinion of one person (individual 'prior') or many people (collective 'prior')**

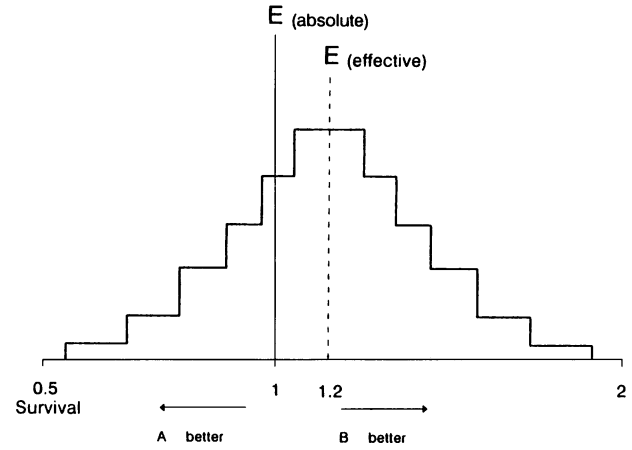

Figure 3 **People may not be able to think of probabilities as a continuum, but rather in categories. If this is true, then there is a range of effects that have equally the greatest probability of occurring—a zone of equivalence in which randomization is ethical. It could be argued that complete equipoise does not exist: that the fact that doctors can 'come off the fence' confirms that they must always have a degree of preference, however slight. However, if a decision must be made, then it will be made, even if the decision maker was previously in 'perfect' equipoise. Here, we make the point that there is likely to be a zone of potential treatment effects to which the mind assigns the same probabilities.**

THE EQUIPOISE CURVE

Effective equipoise occurs when the clinician's 'best bet' about the most likely treatment effect corresponds to the patient's trade-off requirement. As a general rule, as a potential result deviates further from the point of effective equipoise, so the clinician is likely to perceive it as being increasingly unlikely to happen—a curve could be drawn around the point of effective equipoise to represent the distribution of these 'prior' perceptions (Figure 2). It may be wrong to represent these subjective probabilities on a curve, (in reality the mind might perceive zones of equal probability) in which case there is a range of equally likely potential results corresponding to a zone of effective equipoise—a zone of equivalence (Figure 3). Some of the mathematicians, with whom we have discussed our analysis, have become side-tracked with the semantics of the word equipoise, wondering whether it can describe a range of potential outcomes with an equal chance of occurring (as shown in Figure 3) or whether it must be a point and if so, whether one can ever be so agnostic as to be truly 'resting on a fulcrum'. The important point from an ethical perspective is that the clinician has only acted unethically if he or she feels that the principles of trust laid down above have been violated. The Papworth principle (do as you would to a cherished member of your family) is the determining factor. Presumably, clinicians would not wish to see members of their family randomized if, having been previously equipoised, they now had evidence just short of statistical significance. Equally, they may be very happy to offer randomization to a family member over a range of potential effects which they think have an equal probability of occurring (as in Figure 3).

In some cases, the probability envelope may be asymmetrical (Figure 4). In these circumstances, the patient's interests are not served by trial entry, even in the zone of equivalence. This applies when, according, to 'prior' perceptions, a treatment may decrease the risk of a bad outcome but almost certainly will not increase it. An example might be the recently completed Medical Research Council trial of folic acid to prevent neural tube defects: given prior information there was little or no expectation that this treatment might actually increase the risk of *this* outcome. An interesting situation may arise when patients with terminal illness are offered potentially life prolonging therapy. A non-suicidal patient with an expected survival of, say, 2 months may be rationally equipoised when the effect perceived most likely is increased mortality since the 'new' treatment may buy more time if it is beneficial than it stands to deprive the patient of if it is indeed harmful. To give a simple example, if there is a 25% chance that a trial will show an improvement in survival with a new therapy distributed symmetrically around a mean of 12 months versus a 75% chance that it will show a reduced life expectancy distributed around 1 month, then the new therapy may be the best bet, offering an expected net gain of 1.75 months.

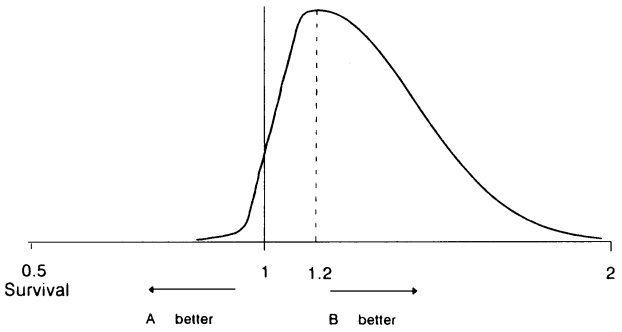

Figure 4 **There is no reason to suppose that potential ('prior') probability estimates of treatment effects should vary symmetrically around the most probable effect. Here an expert (or experts if this is a collective 'prior') believes that the most likely effect is a 20% improvement in survival, that there might well be a greater survival advantage but that a negative effect, though plausible, effect is nevertheless less likely. The many people contemplating trials of mastectomy versus local resection for breast cancer may have had prior equipoise curves such as this**

IMPLICATIONS FOR BAYESIAN TRIAL DESIGN

The accepted technique for the design and interpretation of clinical trials is based on hypothesis testing—the Popperian notion of a null hypothesis underlies much clinical thinking. There is a movement to use an alternative method which seeks simply to describe the probabilities that treatments differ from each other by different amounts. The method is described in detail in statistical texts[28]. Bayesian interpretation of trial results is not dependent on a starting hypothesis, but rather on 'prior' expectations of treatment effects, i.e. on the equipoise 'curve'. Thus, Bayesian approaches incorporate beliefs resulting from evidence external to the trial in a formal way.

If analysis of the results of a trial is to be restricted to this method, then the trial may be 'open', i.e. the results may be made available during the course of the study[29]. This means that equipoise is likely to shift in response to accumulating data, especially if the interval between randomization and outcome is short[30]. At first sight, this suggests that many trials would have to stop at the equivalent of large *P* values in order not to violate the principle of individual equipoise. On the other hand, some clinicians (and their patients) may move into individual effective equipoise as others are moving out. The ethical basis of open trials would then be that different clinical opinions and patient values would, at different times, result in different clinician/patient combinations in effective equipoise. Seen in this light,

different beliefs in the light of the same evidence would not be a problem for scientific medicine, but a benefit. They would allow trials to be done which were ethically acceptable by providing cohorts of doctors/patients who were in equipoise in the face of the same (inconclusive) evidence.

IMPLICATIONS FOR SCIENCE

Our conclusion, that collective and individual equipoise are important principles, is not the best conclusion in a utilitarian sense—at least not in the medium term. This is because utility (the greatest good for the greatest number) would seem to depend on getting precise answers to clinical questions, and this can only happen when 'recruitment' is high. Recruitment may be threatened when importance is attached to equipoise.

As a general rule, many more people stand to benefit from clinical practice which has been improved by strong evidence, than stand to lose by receiving the somewhat less favoured treatment in a clinical trial. Given a 'prior' equipoise curve and an estimate of the number of people who will be treated before a treatment is superseded, it is possible to calculate the thresholds at which more people stand to lose than gain by conducting (or extending) a trial[31]. As a general rule, such calculations favour large trials (i.e. conducted to a high level of precision), because of the huge imbalance that normally exists between the number of people receiving treatment in and outside of clinical trials. If clinicians put individual obligations before their social obligations, then science must pay a price, since equipoise is likely to be disturbed at much lower levels of evidence than would constitute the traditional threshold of scientific 'proof'. In other words, evidence short of the traditional threshold for statistical significance will affect individual equipoise.

Some people may consider it ethically acceptable to make a trade-off between these obligations (social and individual), but we have presented at least one argument against doing this in claiming the primacy of the doctor-patient relationship. Furthermore, it is not clear to us that utility is served by accepting an argument favouring the social obligation over the individual obligation. In the last analysis, the public might become suspicious and resentful if clinicians fail to disclose personal preferences in the interest of science or of convincing other clinicians. If this happened, future patients might withdraw from trials altogether.

Acceptance of our argument might not have as large an effect on trial participation as would at first seem likely. First, we have argued that policy makers are free from the individual obligation and can, with more justification, adopt a consequentialist stance. Furthermore, a reasonable degree of collective equipoise is most likely early in the life of a new treatment. Thus, new treatments can justifiably be restricted, as a matter of public policy, to people in trials. Secondly, trials where one treatment can be substituted for another at a later date are unlikely to be greatly affected by our analysis. Less collective equipoise would seem necessary and patients are less likely to be put off by any personal clinical view favouring one treatment. This is because they can always come back to the alternative method later. Thirdly, doctors who offer trial entry to patients may not be expert in the topic of concern. They may thus be individually equipoised and happy to rely on collective equipoise among those who are regarded as expert. Fourthly, some trials involve randomization of units other than individual participants—wards, clinicians, time periods, general practices and hospital departments can all be randomized in the public interest (of getting precise and accurate information to guide treatment and policy) without violating the trust inherent in the relationship between patients and their doctors. Lastly, 'preference' trials, in which people are invited to choose treatment A, treatment B or a randomized comparison of both treatments, provide an opportunity for all patients to maximize their personal expected utilities while the trial continues to recruit those who are in effective equipoise.

CONCLUSION

Patients are entitled to the most appropriate treatment available. The point of clinical trials is to find out just what is the most appropriate treatment, and would therefore appear not to deny that right. However, in advance of a trial, clinicians will often have rational but different preferences, i.e. they may not be in equipoise.

A degree of collective equipoise among experts is a legitimate requirement for Ethics Committees. However, individual clinicians may have preferences in cases where the evidence is not clear cut. Unless access to the relevant treatment is restricted, we suggest that, the trust between clinician and patient is violated if trial entry is offered in these circumstances (or offered without divulging any clear personal preference). We further suggest that, when treatments have different side effects, the point of individual equipoise is not 'no difference', but 'an effect sufficient to compensate for the treatment with the worst side effect'. Thus, decision analysis defines the treatment of greatest expected utility and trials of life saving, but freely available, treatments are ethical when the treatments under comparison have the same expected utilities.

Acknowledgments Without wishing to ascribe any views to him, we would nevertheless like to acknowledge the helpful discussion with Dr Iain Chalmers over many years. We would also like to acknowledge helpful advice from Dr David Spiegelhalter (MRC Biostatistics Unit, Cambridge), Dr Alistair Hall (Centre for Cardiovascular Studies, Leeds)

and Mr Andrew Vail (Institute of Epidemiology and Health Services Research, Leeds).

REFERENCES

1 Sacks H, Chalmers T, Smith H. Randomised versus historical controls for clinical trials. *Am J Med.* 1982;**72**:233–40

2 Collins R, Doll R, Peto R. Ethics of Clinical Trials. In: Williams CJ, ed. *Introducing New Treatments for Cancer: Practical and Legal Problems.* Chichester: John Wiley & Sons Ltd, 1992:49–66

3 Lockwood M, Anscombe GEM. Sins of omission? The non-treatment of controls in clinical trials. *Aristotelian Soc* 1983;**57**:207–22

4 Freedman B. Equipoise and the ethics of clinical research. *N Engl J Med* 1987;**317**:141–5

5 Kadane JB. Progress toward a more ethical method for clinical trials. *J Med Phil* 1986;**II**:385–404

6 Simes RJ, Tattersall MHN, Coates AS, Raghaven D, Solomon HJ, Smartt H. Randomised comparison of procedures for obtaining informed consent in clinical trials of treatment of cancer. *BMJ* 1986;**293**:1065–8

7 Cassileth BR, Zupkis RV, Sutton-Smith K, March V. Informed consent—Why are its goals imperfectly realised. *N Engl J Med* 1980;**302**(16):896–900

8 Wyld PJ. Informed consent [Correspondence]. *BMJ* 1986;**293**:390

9 Glover J. The MRC and informed consent. *BMJ* 1986;**293**:157–8

10 Johnson N, Lilford RJ, Brazier W. At what level of collective equipoise does a clinical trial become ethical. *J Med Ethics* 1991;**17**:30–4

11 Freedman LS, Spiegelhalter DJ. Application of Bayesian statistics to decision making during a clinical trial. *Statist Med* 1992;**11**:23–35

12 Lilford RJ for the Fetal Compromise Group. Formal measurement of clinical uncertainty: prelude to a trial in perinatal medicine. *BMJ* 1994;**308**:111–12

13 Institute of Medical ethics working party. AIDS, Ethics, and clinical trials. *BMJ* 1992;**305**:699–701

14 MRC Cervical Cerclage Trial. *Br J Obstet Gynaecol* 1988;**95**:437–45

15 Spence J. *The Purpose and Practice of Medicine.* Oxford: Oxford University Press, 1960

16 Gore SM. The consumer principle of randomisation. *Lancet* 1994;**343**:58

17 Korn EL, Baumrind S. Randomised clinical trials with clinician-preferred treatment. *Lancet* 1991;**337**:149–52

18 Challah S, Mays NB. The randomised controlled trial in the evaluation of new technology: a case study. *BMJ* 1986;**292**:877–8

19 Tobias JS, Souhami RL. Fully informed consent can be needlessly cruel. *BMJ* 1993;**307**:1199–201

20 Hellman S. Randomised clinical trials and the doctor-patient relationship: An ethical dilemma [Editorial]. *Cancer Clin Trials* 1979;**2**:189–93

21 Chalmers I. Letter to the editor. *N Engl J Med* 1991;**325**:1514

22 Dudley HAF. Stones, lithotripters, trials, and arguments. *BMJ* 1986;**292**:846–7

23 Lilford RJ, Thornton JG. Decision Logic in Medical practice. *J Coll Physic* 1992;**26**:400–12

24 Lilford RJ. Decision theory to assess delta. *Lancet* 1990;**i**:483–4

25 Lilford RJ, Johnson N. The alpha and beta errors in randomised trials. *New Eng J Med* 1990;**322**:780–1

26 Gilbert J. Patients must be told that treatment will be randomised. *BMJ* 310;**125**:1995

27 Chalmers I, Chalmers T. Randomisation and patient choice. *Lancet* 1994;**344**:892–3

28 Spiegelhalter D, Freedman LS, Parmar MKB. Bayesian approaches to randomised trials. *J R Statist Soc* 1994:**157**(3):357–416

29 Greenhouse JB. On some applications of Bayesian methods in cancer clinical trials. *Statist Med* 1992;**11**:37–53

30 Hughes MD. Reporting Bayesian analysis of clinical trials. *Statist Med* 1993;**12**:1651–63

31 Berry DA, Wolff MC, Sack D. Public health decision making: a sequential vaccine trial. *Bayesian Statist* 1992;**4**:79–96

(Accepted 22 February 1995)